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Metofluthrin

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Overview

Registration Decision for Metofluthrin

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, granted conditional registration for the sale and use of SumiOne Technical Grade and OFF! Clip On Mosquito Repellent, containing the technical grade active ingredient metofluthrin, as a personal mosquito repellent.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

Although the risks and value have been found acceptable when all risk reduction measures are followed, the applicant must submit additional scientific information as a condition of registration.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of SumiOne Technical Grade and OFF! Clip On Mosquito Repellent.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act.*

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "… the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

What Is Metofluthrin?

Metofluthrin is an active ingredient which belongs to the pyrethroid class of insecticides and is used to repel mosquitoes. OFF! Clip On Mosquito Repellent is a battery-powered device that contains a metofluthrin-impregnated cartridge. The OFF! Clip On Mosquito Repellent device is worn on the person and functions as a personal insect repellent by vaporising metofluthrin and emitting it over an area large enough to protect the wearer from mosquitoes.

Health Considerations

Can Approved Uses of Metofluthrin Affect Human Health?

OFF! Clip On Mosquito Repellent containing metofluthrin is unlikely to affect your health when used according to label directions.

Potential exposure to metofluthrin may occur when handling or using the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide-containing products are used according to label directions.

In laboratory animals, metofluthrin was of low acute toxicity by the oral and dermal routes of exposure. It was of slight acute toxicity by the inhalation route of exposure and as such the hazard statement “Caution Poison” is required on the label. Metofluthrin was minimally irritating to the eye, was nonirritating to the skin, and did not cause an allergic skin reaction. Metofluthrin does, however, belong to a class of pesticides that may cause a transient itching, tingling or burning sensation of the skin following skin contact.

OFF! Clip On Mosquito Repellent product consists primarily of metofluthrin; therefore, the toxicity profile and label statements for technical grade metofluthrin are representative of this product.

Registrant-supplied short, and long term (lifetime) animal toxicity tests, as well as information from the published scientific literature were assessed for the potential of metofluthrin to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints for risk assessment included neurotoxicity characterized by clinical signs. In addition, although there was no evidence of increased susceptibility of the young in the guideline toxicity studies submitted, residual uncertainty remains since young animals have differences (such as the age-dependent maturation of key metabolic processes) that may lead to increased susceptibility of the young to pyrethroid

toxicity. There was also evidence of effects on the liver. Longer-term dosing with metofluthrin resulted in liver tumours in rats, but not in mice. The risk assessment protects against the effects noted above by ensuring that the level of exposure to humans is well below the lowest dose at which these effects occurred in animal tests.

Risks in Residential Environments

Risk for residential exposure is not of concern provided that directions specified on the label are observed.

A risk assessment conducted for individuals handling, or those in the vicinity of the OFF! Clip On Mosquito Repellent device, indicated that risks to adults, youth and children are not of concern when the product is used according to label directions.

Environmental Considerations

What Happens When Metofluthrin Is Introduced Into the Environment?

OFF! Clip On Mosquito Repellent will not pose an unacceptable risk to nontarget aquatic and terrestrial organisms.

Metofluthrin enters the environment when used as an insect repellent in a personal device, which allows the active ingredient to vaporize into the air. Significant deposition of metofluthrin in the environment is unlikely due to the volatile nature of the compound, rapid transformation processes in soil, and limited use pattern.

Metofluthrin is highly toxic to aquatic invertebrates, fish, and bees. But the exposure of these nontarget organisms to metofluthrin is, however, unlikely based on the use pattern.

Value Considerations

What Is the Value of OFF! Clip On Mosquito Repellent?

OFF! Clip On Mosquito Repellent is a personal insect repellent device that provides protection from mosquitoes for up to 11 hours.

Mosquitoes are an outdoor nuisance pest across all of Canada, especially in the morning and evening. Mosquito bites can cause discomfort and irritation, and can vector diseases such as West Nile Virus and other encephalitis-causing viruses. In addition to health risks associated with mosquito bites, annoyance from mosquitoes can reduce the enjoyment of being outdoors and cause people to avoid outdoor activities when mosquito populations are heavy.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of OFF! Clip On Mosquito Repellent to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

For OFF! Clip On Mosquito Repellent the hazard statement "Caution Poison" is required on the product label, as is the statement "only adults are permitted to replace the refill disk." In addition, a statement identifying that the device "should not be worn while barbecuing" is required.

Environment

Key risk-reduction measures for the protection of the environment include precautionary label statements:

- Toxicity statement for bees;
- Toxicity statement for aquatic organisms.

What Additional Scientific Information Is Being Requested?

Although the risks and value have been found acceptable when all risk-reduction measures are followed, the applicant must submit additional scientific information as a condition of registration. More details are presented in the Science Evaluation of this Evaluation Report or in the Section 12 Notice associated with these conditional registrations. The applicant must submit the following information within the time frames indicated.

Human Health

To further confirm the units of exposure and dermal absorption value used in the risk assessment, conditional registration of the OFF! Clip On Mosquito Repellent can be supported pending the submission of the following:

- New passive dosimetry study to estimate the amount of metofluthrin deposited on the surface of the skin and the amount of the chemical available for inhalation through the use of appropriate trapping devices for both adults and children. The study must be done according to acceptable guidelines.

- New in vivo dermal absorption study to estimate the dermal absorption of metofluthrin with longer monitoring periods to better determine the fate of the skin bound residues. The study must be done according to acceptable guidelines.

Other Information

As these conditional registrations relate to a decision on which the public must be consulted,[3] the PMRA will publish a consultation document when there is a proposed decision on applications to convert the conditional registrations to full registrations or on applications to renew the conditional registrations, whichever occurs first.

The test data cited in this Evaluation Report (for example, the test data relevant in supporting the registration decision) will be made available for public inspection when the decision is made to convert the conditional registrations to full registrations or to renew the conditional registrations (following public consultation). If more information is required, please contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (pmra.infoserv@hc-sc.gc.ca).

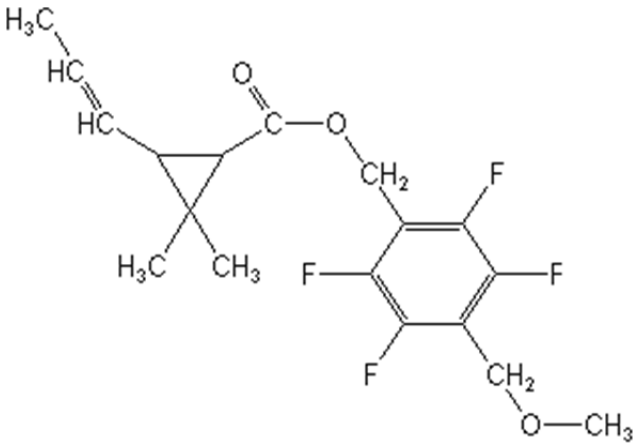
[3] As per subsection 28(1) of the *Pest Control Products Act.*

Science Evaluation

Metofluthrin

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Metofluthrin
Function	Insect repellent
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	2,3,5,6-tetrafluoro-4-(methoxymethyl)benzyl (*EZ*)-(1*RS*,3*RS*;1*RS*,3*SR*)-2,2-dimethyl-3-(prop-1-enyl)cyclopropanecarboxylate OR 2,3,5,6-tetrafluoro-4-(methoxymethyl)benzyl (*EZ*)-(1*RS*)-*cis*-*trans*-2,2-dimethyl-3-prop-1-enylcyclopropanecarboxylate
2. Chemical Abstracts Service (CAS)	[2,3,5,6-tetrafluoro-4-(methoxymethyl)phenyl]methyl 2,2-dimethyl-3-(1-(propenyl)cyclopropanecarboxylate
CAS number	240494-70-6
Molecular formula	$C_{18}H_{20}F_4O_3$
Molecular weight	360.34
Structural formula	
Purity of the active ingredient	96.65%

1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product

Technical Product—SumiOne Technical Grade

Property	Result
Colour and physical state	Colourless liquid
Odour	Slight odour
Melting point	-54.92°C
Boiling point	340.36°C
Relative density at 20°C	1.21
Vapour pressure	Temp (°C) Vapour pressure (Pa) 20 8.969×10^{-4} 25 1.896×10^{-3}
Henry's law constant at 25°C	1/H= 1.754×10^{3} at 25ºC
Ultraviolet (UV)-visible spectrum	Not expected to absorb at $\lambda > 300$ nm
Solubility in water at 20°C	0.441 mg/L
Solubility in organic solvents at 20°C (g/100 mL)	Solubility is >250 g/L for n-heptane, 1,2-dichloroethane, acetone, p-xylene, methanol and ethyl acetate
n–Octanol-water partition coefficient	Log K_{ow} = 4.88
Dissociation constant (pK_a)	No dissociation detected between pH 1-13
Stability (temperature, metal)	Stable to metals and metal ions at ambient or elevated temperature (54°C) for 14 days

End-Use Product—OFF! Clip On Mosquito Repellent

Property	Result
Colour	Clear (liquid impregnated onto pad)
Odour	Odourless (liquid impregnated onto pad)
Physical state	Liquid (impregnated onto pad)
Formulation type	Impregnated fabric
Guarantee	14.5 mg metofluthrin
Container material and description	Plastic battery operated device (2 AAs) with polyester fabric substrate refill cartridge
Density	1.21 g/mL (liquid impregnated onto pad)
pH of 1% dispersion in water	N/A
Oxidizing or reducing action	N/A
Storage stability	Stable (within certified limits) over 12 months in commercial packaging at ambient conditions protected from light
Corrosion characteristics	Not corrosive to commercial packaging
Explodability	N/A

1.3 Directions for Use

OFF! Clip On Mosquito Repellent is a personal insect repellent for use outdoors that repels mosquitoes for up to 11 hours. To use OFF! Clip On Mosquito Repellent, a mosquito repellent disk is inserted into the battery-powered device. The device is then turned on and clipped onto the user's belt, pants, shorts, waistband, or purse. OFF! Clip On Mosquito Repellent requires several minutes to provide mosquito repellency after being turned on or after moving to a new location. If the device is turned off before 11 hours have elapsed, the remainder of the repellent can be used at a future time.

1.4 Mode of Action

The OFF! Clip On Mosquito Repellent device vaporises and emits metofluthrin, a pyrethroid insect repellent, from a repellent-impregnated cartridge into an area large enough to protect the wearer. While mosquitoes are repelled from the treated area, the specific mode of action by which metofluthrin vapours repel mosquitoes is not certain.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in SumiOne Technical Grade have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for Residue Analysis

Gas chromatography methods with mass spectrometry (GC-MS) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in animal matrices and environmental media. Methods for residue analysis are summarized in Appendix I, Table 1.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Metofluthrin is a fluorinated synthetic pyrethroid that operates via a neurotoxic mode of action in insects and mammals. Pyrethroids delay the closing of neuronal voltage-dependent sodium channels causing the depolarization of the neuron; this interferes with the ability of the nervous system to relay nerve transmissions and results in downstream clinical effects. As a type I pyrethroid, metofluthrin displays aspects of the neurotoxicity syndrome known as the "T syndrome", which is characterized in rodents by aggressive sparring, increased sensitivity to stimuli, and fine whole body tremor.

A detailed review of the toxicological database for metofluthrin was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. A waiver for the requirement of a 90-day inhalation study was accepted for the purposes of the current registration petition. Additional studies were submitted which served to bridge the original database to a slightly different specification of metofluthrin. Overall, the studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices (GLP). The scientific quality of the data is high and the database is considered adequate to define the majority of toxic effects that may result from exposure to metofluthrin.

Following oral dosing in rats with metofluthrin radiolabelled in two positions, absorption was rapid and moderately high for both sexes. The area-under-the-curve was slightly higher for females than males, suggesting a higher systemic exposure. Excretion of the carbonyl radiolabel occurred primarily via the urine. The methoxymethylbenzyl radiolabel was excreted in similar amounts in urine and feces. A significant amount of radioactivity was excreted via the bile. Excretion was essentially complete by 24 hours. Metofluthrin was extensively metabolized with 46 metabolites characterized. The parent compound was detected in feces but not in urine or bile. Distribution of metofluthrin was rapid to all tissues, with the liver, followed by the kidney, containing the highest concentrations of radioactivity. Repeat-dose administration did not reveal any evidence of bioaccumulation. The proposed biotransformation pathways of metofluthrin included cleavage of the ester linkage, oxidation of the methyl groups on the benzyl moiety to form alcohol, aldehyde and carboxylic acid metabolites, reduction of the double bond in the acid moiety of the molecule, and formation of glutathione and sulphate adducts.

In the rat, technical grade metofluthrin was of low acute toxicity via the oral and dermal routes, and of slight acute toxicity via the inhalation route. Clinical signs consisted of those indicative of pyrethroid neurotoxicity (salivation, tip toe gait, soft stool, urinary incontinence, tremors and clonic convulsions). Metofluthrin was minimally irritating to the eyes and nonirritating to the skin of rabbits. It was not a dermal sensitizer in guinea pigs using the Maximization method. A phototransformation breakdown product of the technical, MFFO, had a similar acute toxicity profile. The end-use product OFF! Clip On Mosquito Repellent consists primarily of metofluthrin and, therefore, the acute toxicity profile of technical grade metofluthrin was considered representative of this product.

Repeat-dose studies were conducted via the oral dietary (rat, mouse), oral capsule (dog), dermal (rat) and inhalation (rat) routes of exposure. Neurotoxicity was a critical effect observed throughout the database. Clinical signs of neurotoxicity were observed in rats (tremors, twitches, tiptoe gait, clonic convulsion, death) and dogs (tremors, vomiting). In short-term dietary studies, body tremors usually occurred early in the study and disappeared with increasing dosing duration. In rats, tail tremors, tiptoe gait, and clonic convulsions were noted following inhalation exposure in addition to mortality, decreased body weight, liver hypertrophy and increased liver weight. Tremors and salivation were noted in rats following repeat-dose dermal administration. Hyperactivity and vocalization were also observed in the dermal toxicity study. These effects were observed early in the study and only prior to removal of the test chemical from the skin at the end of the 6-hour contact period. For this reason, the observations were considered likely to be the result of paresthesia. Mortality was observed at high doses in the rat via all routes of exposure and was often preceded by clinical signs of neurotoxicity. In the 90-day and 12-month dog capsule studies, tremors in high-dose animals were observed after a few doses. At lower doses, tremors were also observed, but they occurred later in the study and were transient in nature. Frequent and consistent vomiting was noted in both sexes for mid- and high-dose animals throughout the dosing period which could be attributed to neurotoxic effects. There were no neurotoxic effects noted in the repeat dose studies in the mouse. Overall, increased duration of dosing did not result in a pronounced increase in the severity or nature of the neurotoxic effects noted.

In acute neurotoxicity testing in rats, clinical and behavioral signs including increased motor activity, tremors, twitches, tachypnea and death were observed at the high dose. In repeat-dose neurotoxicity testing, clinical signs of toxicity such as soft or liquid feces, or scant feces in male rats and tremors and twitches and death in female rats, were observed at high doses. Decreased body weight along with decrements in food consumption was also observed. There was no evidence of neuropathology in either study.

Liver effects attributed to metofluthrin administration were most pronounced in rats, but were also exhibited in mice. In repeat-dose studies in rats, increased liver weights, centrilobular hepatocellular hypertrophy and increased smooth endoplasmic reticulum (SER) were consistently evident after brief durations of dosing (7 days). Supplemental studies demonstrated that cytochrome P450 liver enzymes (CYP2B1/2 and CYP3A1) were also elevated at this time-point. Alterations in clinical chemistry parameters became apparent with increased duration of dosing in the rat, and liver findings progressed to altered hepatocellular foci, liver nodules and neoplastic lesions following chronic dosing. Increased liver weights, hepatocellular hypertrophy, and liver clinical chemistry changes were also observed in mice, along with an increase in Kupffer cells as well as liver degeneration and necrosis following intermediate-term dosing. Apart from increased liver weights in female mice, liver effects were not observed following long-term administration of metofluthrin in the mouse, although lower dose levels were tested in the long-term study compared to those tested in the 90-day study.

Other effects noted in the database included evidence of nephrotoxicity in the rat, but only after long-term exposure to metofluthrin, as evidenced by increased kidney tubular vacuolation, tubular casts, and interstitial fibrosis. In dogs, a number of organ weight changes at the high dose were without histopathological correlates. Following chronic administration to mice, body weight changes were observed along with lung congestion and discolouration as well as increased heart weights. Treatment-related effects in mice were observed at higher doses than those producing effects in the other species, indicating that mice were less sensitive than the other species to the toxic effects of metofluthrin.

In the rat dietary multigeneration reproduction study, parental toxicity was evident with soft/liquid feces, salivation, tremor/twitches, and chromorhinorrhea observed at the mid-dose. Decreased body weight and body-weight gain was also observed in the dams during gestation and lactation. Liver effects were observed in both sexes and manifested as increased liver weight and hepatocellular hypertrophy. At the highest dose, increased weights in pituitary, uterus, and oviducts were noted as well as a decreased follicle count (first generation only). Toxicity to the offspring was noted at the same dose levels at which parental toxicity occurred and hence the young animal was not more sensitive to metofluthrin toxicity than the adult animal in this assay. Delayed preputial separation was noted at the mid-dose and above. Delayed onset of vaginal patency was recorded in the F^1 generation as were decreased mean litter size and a reduced lactation index. Offspring were also noted with clinical signs indicative of neurotoxicity including dehydration, cold to touch, and whole body tremors. Pups displayed decreased body weight during lactation as well as decreased brain and thymus weights. In a supplemental dietary one-generation reproduction study using lower dose levels, additional behavioral testing was conducted on weanlings 4-6 weeks of age. There were no adverse findings in sensory function or conditional avoidance testing, or in the open-field test. However, the behavioral assessments were not conducted at the time-to-peak effect in offspring. There was no effect on genital development or on subsequent mating in these weanlings.

The developmental toxicity of metofluthrin was investigated in rats and rabbits following gavage dosing. In rats, the most notable sign of toxicity in the dams was tremors, starting shortly after dosing (2 to 3 hours) and lasting 1 to 3 days. In rabbits, some deaths occurred in dams at the higher doses. No developmental effects were observed in fetuses and sensitivity of the young was not identified in either study.

Despite a lack of evidence of increased sensitivity of the young in any of the submitted studies, residual uncertainty remains regarding susceptibility of the young. Literature studies indicate that pharmacodynamic and pharmacokinetic factors, notably age-dependent maturation of key metabolic processes, may lead to increased susceptibility of the young to pyrethroid toxicity. Young animals have incomplete maturation of the enzyme systems that detoxify pyrethroids, particularly the carboxylesterases and cytochrome P450s. Consequently, pyrethroid concentrations in target tissues (for example, brain) may be higher in young animals than in adults given the same dose. Pyrethroid neurotoxicity is correlated with peak concentrations of the compound, with gavage dosing patterns resulting in greater internal peak doses compared to dietary administration. The pyrethroids are regarded as having a narrow window of time-to-peak-effect. Behavioral assessments conducted in the supplemental reproduction study were not conducted at the time-to-peak effect in offspring and neither the acute nor the short-term neurotoxicity study considered time-to-peak effect. Although a developmental neurotoxicity

study was not submitted, the design of such a study would not consider time-to-peak-effect and may miss the window of peak toxicity for the pyrethroids (Scollon 2010). Therefore, the uncertainty regarding potential sensitivity of the young has been reflected in the form of a database uncertainty factor, pending the development of an appropriate study protocol.

Metofluthrin was determined to be nongenotoxic in the battery of genotoxicity studies. There was no evidence of carcinogenic potential in the mouse. In the rat oral chronic toxicity/carcinogenicity study, there was a treatment-related increase in the incidence of liver adenomas and carcinomas. A mode of action (MOA) similar to that of phenobarbital was proposed for tumor induction. A description of key events, with dose and temporal relationship was presented and several mechanistic studies to support the MOA were provided. The mechanistic studies suggested that metofluthrin produces liver effects (increased liver weight, hepatocellular hypertrophy, increased smooth endoplasmic reticulum and increased CYP mRNA and protein levels) that are similar to those induced by phenobarbital. However, in experiments with metofluthrin using Bromodeoxyuridine (BrdU) labeling, there was no clear relationship between cell proliferation and dose, with highly variable data not allowing for a clear interpretation. Protein measurements in rats exposed to metofluthrin did not demonstrate the expected increase in microsomal and P450 protein levels which were clearly demonstrated in rats exposed to phenobarbital. Activation of constitutive androstane receptor, indicated as a key event in tumor formation, was demonstrated through increased CYP 2B1/2 mRNA levels in metofluthrin treated rats. However, mRNA levels were not consistently elevated at doses where tumors were noted. Treatment with metofluthrin affects many of the same parameters altered by phenobarbital; however, the magnitude of change was much lower for metofluthrin-treated animals. The converse was demonstrated with regards to tumour profiles for both chemicals. Treatment with metofluthrin produced a high number of hepatocellular carcinomas in rats whereas phenobarbital is not known to increase carcinomas in rats. Although the MOA was deemed plausible, the overall weight of evidence to support it was deemed inadequate. Consequently, a linear low-dose extrapolation for the cancer risk assessment was employed.

Results of the toxicology studies conducted on laboratory animals with metofluthrin, the phototransformation breakdown product of metofluthrin (MFFO), and the associated metofluthrin end-use product, are summarized in Appendix I, Tables 2-4. The toxicology endpoints for use in human health risk assessment are summarized in Appendix I, Table 5.

Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents to the PMRA, including adverse effects to Canadian health and the environment. Incidents were searched and reviewed for the active metofluthrin. At the time of product registration in 2011, there were no incident reports identified to the PMRA. As of 4 March 2015, there were 15 human and one domestic animal incident reports as well as seven packaging failure reports involving metofluthrin in the PMRA database. All reported incidents were associated with the product OFF! Clip On Mosquito Repellent.

3.1.1 *Pest Control Products Act* Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the standard complement of required studies including developmental toxicity studies in rats and rabbits, and a reproductive toxicity study in rats. In addition, a supplemental reproductive toxicity study in rats was provided.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased susceptibility of fetuses or offspring compared to parental animals in the reproductive and prenatal developmental toxicity studies. In the reproduction study, offspring effects included delayed sexual maturation as well as reduced body weights, litter size and lactation index. Clinical signs of neurotoxicity as well as decreased brain and thymus weights were also recorded. All of these findings occurred at doses at which parental toxicity was observed. There was no evidence of effects on fetuses in either developmental toxicity study.

Young animals have incomplete maturation of enzyme systems which detoxify pyrethroids and, thus, may be more susceptible due to higher and prolonged brain concentrations, compared to adults (Kim et al. 2010). Due to the lack of a comparative oral neurotoxicity study, an adequate assessment of sensitivity of the young is currently not available and residual uncertainty remains concerning susceptibility of the young to potential neurotoxic effects. This concern was reflected through the use of a database uncertainty factor of threefold in the risk assessment. Since these concerns were addressed with a database uncertainty factor, the *Pest Control Products Act* factor was reduced to onefold.

3.2 Acute Reference Dose (ARfD)

With respect to the proposed use, establishment of an ARfD was not required as there are no food uses or potential for contamination of drinking water sources.

3.3 Acceptable Daily Intake (ADI)

With respect to the proposed use, establishment of an ADI was not required as there are no food uses or potential for contamination of drinking water sources.

Cancer Assessment

The unit risk for metofluthrin, denoted by q_1^* (representing the upper 95% confidence limit on the slope of the dose-response curve in the low-dose region) was calculated on the basis of data from the rat chronic toxicity/carcinogenicity study. The most potent unit risk, 1.13×10^{-2}(mg/kg bw/day)$^{-1}$, was calculated on the basis of the combined incidence of hepatocellular adenomas/carcinomas in female rats.

3.4 Residential Risk Assessment

Residential exposure to OFF! Clip On Mosquito Repellent is considered intermediate in duration and is predominantly by the dermal, inhalation and incidental oral routes.

3.4.1 Toxicological Endpoints

Short-term to Intermediate-term Dermal Exposure

For short- to intermediate-term dermal risk assessment for all populations, the 90-day dermal toxicity study in rats was selected. In this study, the no observed adverse effect level (NOAEL) was determined to be 300 mg/kg bw/day based on mortality, clinical signs and an increased incidence of squamous cell hyperplasia of the skin at the lowest observed adverse effect level (LOAEL) of 1000 mg/kg bw/day. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, residual uncertainty regarding susceptibility of the young has been captured as a database uncertainly factor (UF_{DB}) of threefold. Consequently, the *Pest Control Products Act* factor was reduced to onefold. The target margin of exposure (MOE) is 300.

Short-term to Intermediate-term Inhalation Exposure

In selecting an endpoint for short- to intermediate-term inhalation risk assessment for all populations, the following was considered. The use season has been characterized as approximately four months in duration. A 90-day inhalation study was not available. However, the database contains a 28-day inhalation study. In this study, the no observed adverse effect concentration (NOAEC) was determined to be 0.10 mg/L air (equivalent to a NOAEL of 17 mg/kg bw/day) based on mortality, clinical signs of neurotoxicity, liver effects, and decreased body weight noted at the lowest observed adverse effect concentration (LOAEC) of 0.20 mg/L air (equivalent to a LOAEL of 35 mg/kg bw/day). Clinical signs of neurotoxicity, a critical endpoint in the inhalation study, were evident via both the inhalation and oral routes of exposure. In dietary studies of up to six (rats) or 18 (mice) months in duration, there did not appear to be an increase in toxicity with increased duration of dosing. A similar comparison of toxicity in dogs revealed tremors occurring at a lower dose in the 12-month capsule study as compared to the dose producing tremors in the 90-day capsule study. Tremors at the lower dose in the 12-month dog study were transient and occurred mainly beyond the proposed duration of use. In light of all of this information, it was concluded that the results of the 28-day inhalation study were appropriate for use in the present risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied to the NOAEL from the 28-day study. As discussed in the *Pest Control Products Act* Hazard Characterization section, residual uncertainty regarding susceptibility of the young has been captured as an UF_{DB} of threefold. Consequently, the *Pest Control Products Act* factor was reduced to onefold. The target MOE is 300.

Short-term Incidental Oral Exposure

For short-term incidental oral exposure, the gavage developmental toxicity study in rats was selected. In this study, the NOAEL was 15 mg/kg bw/day based on tremors in the dams at the LOAEL of 30 mg/kg bw/day. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, residual uncertainty regarding susceptibility of the young has been captured as an UF_{DB} of threefold. Consequently, the *Pest Control Products Act* factor was reduced to onefold. The target MOE is 300.

3.4.1.1 Dermal Absorption

Two groups of two male Charles River rats were dermally administered methoxymethylbenzyl-α- ^{14}C-labelled S-1264, at a single dose of 0.002 mg/cm^2 (0.02 mg/50µL administered to a skin surface area at 10 cm^2). Goup A was exposed for six hours whereas Group B was exposed for 24 hours. After exposure, rats were anaesthetized, skin was washed and excised then rats were sacrificed. Radiolabelled residues were collected and measured as percent of the applied dose.

A major limitation of the study was that only one dose was selected which was higher than the expected exposure from the proposed product. Therefore, the study did not span the range of doses expected in the field. It is not known whether doses below the tested dose would result in a higher dermal absorption value. Another major limitation was the use of only two animals per exposure duration which limits the statistical significance of the results.

Total recovery of the applied dose (mass balance) was 94.8% and 91.7% for the six-hour and 24-hour exposure groups, respectively. The recoveries were considered within the acceptable range (70–120%) for both groups. Results were not adjusted for incomplete recovery of the applied dose.

Results showed total change in residue distribution with increasing hours of exposure. Urine residues increased ten folds (1.2 to 10.2%), carcass residues increased from 3.6 to 6.2%, protective covering residues increased from 1.2 to 3.7%, and feces residues increased from <LOQ to 1.0%. Lower recoveries were noted in the blood (0.1%) which did not change with increase hours of exposure. Since only one dose was tested in this study and only two animals were included for each duration, the overall dermal absorption may be under estimated.

The skin wash residues dropped significantly (from 67.6 to 40.3%) with increasing exposure duration from six to 24 hours while the majority of absorbed dose remained bound to the skin (21.2 and 30.2 % of the applied dose, respectively). Therefore, some of the skin bound residues appear to have been absorbed. Since a longer exposure duration was not tested, and considering the limitations of the study, the skin bound residues will be added to the absorbed residues.

The total absorbed dose was calculated by summing the excreted residues (urine, feces, cage wash) plus absorbed residues (carcass, blood) and the skin bound residues at the application site. An estimate of dermal absorption value was determined to be 48% based on the highest total absorbed dose found after 24 hours of exposure.

This value is considered to be conservative as it includes the skin bound residues that might not all be systemically available. However, this value may not adequately reflect absorption at lower dose levels. In the absence of a guideline approved study this value could be used for deriving systemic doses of dermal deposition; however, there is very limited confidence in the dermal absorption value.

3.4.2 Residential Exposure and Risk

3.4.2.1 Residential Handler Exposure and Risk Assessment

Adults
There is potential for dermal exposure to (adult) homeowners inserting or replacing the cartridge containing metofluthrin in the device. This exposure is expected to be short-term in duration.

Table 3.4.2.1 Adult handler dermal non cancer and cancer exposure

Amount of metofluthrin in cartridge (mg)	Fraction of transferable residues (%)[1]	No. of cartridges used/day	Exposure (mg/kg bw/day)[2]	MOE[3] (Target MOE = 300)	Average Daily Dose[4] (ADD; mg/kg bw/day)
16.5	1	1	2.36×10^{-3}	127 000	1.13×10^{-3}

1. Fraction of transferable residue is assumed to be 1% according to the USEPA Residential SOP (1997) for dog collar, as the paper impregnated with metofluthrin is similar to the impregnated dog collar.
2. Exposure = $\frac{\text{Amount of a.i. in cartridge} \times \text{Fraction transferable residue} \times \text{No. of cartridges used /day}}{\text{BW(70kg)}}$

3. MOE = $\frac{\text{NOAEL (300 mg/kg bw/day)}}{\text{Exposure}}$

4. ADD = $\frac{\text{Amount of a.i. in a cartridge} \times \text{Fraction transferable residue} \times \text{No. of cartridge used /day} \times \text{DA}}{\text{BW (70kg)}}$

Youth and Children
The label states to keep out of reach of children. Since it is considered unlikely for youth and children to replace the cartridge (refill disk), and in order to exclude this activity from being considered in the risk assessment for youth, the following statement will be added to the label "only adults are permitted to replace the refill disk."

3.4.2.2 Postapplication Residential Exposure and Risk

OFF! Clip On Mosquito Repellent is a continuous action battery powered device containing a metofluthrin-impregnated cartridge that is inserted into the device and then disposed of when empty. An electric fan drives air flow across the cartridge. The device that clips onto a belt, pants, shorts, waistband, or purse is designed to provide up to 11 hours of outdoor mosquito protection for the person using the device. The device is to be refilled only by an adult, but may be used by children or youth. The purpose of the passive dosimetry study was to estimate the inhalation and dermal exposures of a homeowner wearing the device as well as bystander exposure.

The nonGLP compliant chemical specific passive dosimetry exposure study was conducted in an outdoor setting at one location on a patio of a private residence in California on three separate evenings between September until November 2004. Instead of human subjects, an adult and a child size manikin were used. The device was placed only on the adult size manikin at waist level. To monitor the dermal and inhalation exposures, the adult manikin was covered with an inner dosimeter and a commercially available OVS sorbent air sampling tube placed at the height of 1.5 m (breathing zone level of an adult). The child manikin was monitored only with an air sampling tube placed at the height of 1.1 m (breathing zone level of a child). The air sampling tubes were connected to air sampling pumps with air intake of 2 L/min**.** At zero tothree hours and three - six hours after activating the device on the adult manikin, air samples were collected from both sorbent tubes and analyzed for metofluthrin residues by GC analysis. At the end of six hours exposure, seven patches (5cm × 5cm pieces) from different locations on the inner dosimeter of the adult manikin were cut off and analyzed for metofluthrin residues. Whole dosimeter was not analyzed. Hands, head, face and neck were not monitored. At the end of six hours exposure period, the device was wiped twice with gauze wetted with dioctyl sodium sulfosuccinate (DSS, simulating saliva) or isopropyl alcohol (IPA). All matrices were collected on three separate days. Meteorological data (temperature, humidity and wind velocity) were collected during the field phase of the study.

Based on the EPA 875 Occupational and Residential Exposure Test Guidelines, several limitations were noted in the study. The study used manikins; therefore, the data are not relevant to humans performing outdoor activities. The study was not conducted under GLP guidelines and no study protocol was provided. Hence, the validity of the design, the quality control and the usefulness of data generated from the study are questionable. Instead of several locations, data were collected from one location only and from one dosimeter only instead of a minimum of 10 subjects. SumiOne form of metofluthrin, S-1264, used in the study is different from SumiOne-Z form, S-1264ZR, proposed to refill the device cartridge for use in Canada. Field fortification levels for all matrices were higher (2× – 200×) than the range of residues detected in field samples. The mean recovery of the low level (20X LOQ) field fortified dosimeter samples was 51.35 ± 25.82% (< acceptable range of 70–120%) with a coefficient of variation of 50%. All samples were transferred the following day to the analytical laboratory and analyzed. Patches of the dosimeter were analyzed in triplicate. No outer dosimeter was used and no hand (gloves), face, neck and head sampling was conducted. Therefore, total exposures could not be calculated.

Even though the study had several major limitations, the study was used to assess exposure to the personal insect repellent containing metofluthrin.

3.4.2.2.1 Adult – Postapplication Exposure and Risk Assessment

Postapplication dermal and inhalation exposure considers a consumer wearing the OFF! Clip On Mosquito Repellent device while engaging in outdoor activities. The label states “Do not cover the device when in use or place it near sources of heat or ignition” and since barbecuing is a common activity in outdoor areas, a label amendment will be required**.**

There is potential for dermal and inhalation exposure to consumers wearing OFF! Clip On Mosquito Repellent. The exposure duration will be considered intermediate as it is used during the four months of mosquito season for 12-hours/day according to the DEET insect repellent risk assessment from the DEET joint venture (RRD2002-01, *Personal insect repellents containing DEET (N,N-diethyl-m-toluamide and related compounds*).

Dermal and inhalation exposure during the use of the device

Postapplication dermal and inhalation exposure was estimated by coupling the units of exposure values from the passive dosimetry study with the amount of product handled per day. Given the nature of clothing that is normally worn while engaging in outdoor activities, the shorts and short-sleeved shirt scenario was chosen. For the part of the body that is covered, a protection factor of 50% (according to NAFTA harmonization document used by USEPA for the addition of single layer permeable clothing when monitoring data are unavailable) was applied to the units of exposures (Appendix 1, Table 6).

Although all the inhalation results in the passive dosimetry study for adults were non-detect, inhalation exposure was based on ½ LOQ.

Table 3.4.2.2 Non cancer dermal and inhalation exposure

Non cancer dermal and inhalation exposure								
Dermal units of exposure[1] (UE; µg/kg a.i. handled)	**Inhalation units of Exposure[1] (UE; µg/kg a.i. handled)**	**Amount of metofluthrin in cartridge (mg)**	**No. of cartridges used/day**	**Dermal Exposure[2] (mg/kg bw/day)**	**MOE[3] (Target MOE = 300)**	**Inhalation Exposure [2] (mg/kg bw/day)**	**MOE[3] (Target MOE = 300)**	**Combined MOE[4]**
39751840	79200	16.5	1	9.37×10^{-3}	32 000	1.87×10^{-5}	932 000	31 000

1. Dermal and inhalation units of exposures: See Appendix I, Table 6
2. Dermal and Inhalation Exposures = $\frac{\text{UE} \times \text{Amount a.i./cartridge} \times \text{No.of cartridges used/day} \times \text{conversion factor}}{\text{BW (70 kg)}}$
3. MOE = $\frac{\text{NOAEL}}{\text{Exposure}}$
4. Combined MOE = $\frac{1}{1/\text{MOE dermal} + 1/\text{MOE Inhalation}}$

Table 3.4.2.3 Cancer dermal and inhalation exposure

Cancer dermal and inhalation exposure					
Dermal units of exposure[1] (UE; µg/kg a.i. handled)	**Inhalation units of exposure[1] (UE; µg/kg a.i. handled)**	**Amount of metofluthrin in cartridge (mg)**	**No. of cartridges used/day**	**Dermal Average Daily Dose[2] (ADD; mg/kg bw/day)[2]**	**Inhalation Average Daily Dose [3] (ADD; mg/kg bw/day)[3]**
39751840	79200	16.5	1	4.5×10^{-3}	1.87×10^{-5}

1. Dermal and inhalation units of exposures: See Appendix I, Table 6
2. Dermal ADD = $\frac{\text{Dermal UE} \times \text{Amount a.i./cartridge} \times \text{No.of cartridges used/day} \times \text{conversion factors} \times \text{DA (48\%)}}{\text{BW (70 kg)}}$
3. Inhalation ADD = $\frac{\text{Inhalation UE} \times \text{Amount a.i./cartridge} \times \text{No.of cartridges used/day} \times \text{conversion factor}}{\text{BW (70 kg)}}$

For incidental exposure to residues on the surface of a device during its use, incidental dermal exposure, expected from touching the device, was estimated using the passive dosimetry study which measured the total amount of residues accumulating on the device per hour.

Table 3.4.2.4 Incidental noncancer and cancer dermal exposure

Potentially transferable residue (µg/kg a.i. handled)	Amount of metofluthrin in cartridge (mg)	No. of cartridges used/day	Exposure (mg/kg bw/day)[2]	MOE[3] (Target MOE = 300)	Average Daily Dose[4] (ADD; mg/kg bw/day)
239333	16.5	1	5.64×10^{-5}	5 320 000	2.71×10^{-5}

1. Potentially transferable residue (see Appendix I, Table 6)
2. Exposure = $\frac{\text{Potentially transferable residue} \times \text{Amount a.i./cartridge} \times \text{No.of cartridges used/day} \times \text{conversion factor}}{\text{BW (70 kg)}}$
3. MOE = $\frac{\text{NOAEL (300 mg/kg bw/day)}}{\text{Exposure}}$
4. ADD = $\frac{\text{Potentially transferable residue} \times \text{Amount a.i./cartridge} \times \text{No.of cartridges used/day} \times \text{conversion factor} \times \text{DA (48\%)}}{\text{BW (70 kg)}}$

3.4.2.2.2 Youth – Postapplication Exposure and Risk Assessment

Since the label does not prohibit the use by youth, these individuals may be exposed to metofluthrin when wearing OFF! Clip On Mosquito Repellent while engaging in outdoor activities.

Similar to adults, the exposure duration was considered intermediate as the clip on is used during the four months of mosquito season per year for 12 hours/day, according to the DEET insect repellent risk assessment from DEET joint venture (RRD2002-01, *Personal insect repellents containing DEET (N,N-diethyl-m-toluamide and related compounds)*.

For dermal and inhalation exposure during the use of the device, a postapplication dermal exposure was estimated by coupling the units of exposure values from the passive dosimetry study (adjusted for youth (6 to 12 years) based on an average surface area of 12650 cm^2 (NAFTA)) with the amount of product handled per day. Given the nature of clothing that is normally worn while engaging in outdoor activities, shorts and short sleeved shirt scenario were chosen from the USEPA Residential SOP (2009). For the part of the body that is covered a protection factor of 50% (according to NAFTA harmonization document used by USEPA for the addition of single layer permeable clothing when monitoring data are unavailable) was applied to the units of exposures (Appendix I, Table 6).

Although all the inhalation results in the passive dosimetry study for adults were non-detect, inhalation exposure was based on ½ LOQ.

Table 3.4.2.5 Non cancer dermal and inhalation exposure

Non cancer dermal and inhalation exposure								
Dermal Units of exposure[1] (µg/kg a.i. handled)	**Inhalation Units of exposure[1] (µg/kg a.i. handled)**	**Amount of metofluthrin in cartridge (mg)**	**No. of cartridges used/day**	**Dermal Exposure (mg/kg bw/day)[2]**	**MOE[3] (Target MOE = 300)**	**Inhalation Exposure (mg/kg bw/day)[2]**	**MOE[3] (Target MOE = 300)**	**Combined MOE**
27270107	79200	16.5	1	1.15×10^{-2}	26 000	3.35×10^{-5}	519000	25 000

1. Dermal and inhalation units of exposure: See Appendix I, Table 6
2. Dermal and Inhalation Exposures = $\frac{\text{UE} \times \text{Amount a.i./cartridge} \times \text{No.of cartridges used/day} \times \text{conversion factor}}{\text{BW (39 kg)}}$
3. MOE = $\frac{\text{NOAEL}}{\text{Exposure}}$
4. Combined MOE = $\frac{1}{1/\text{MOE dermal} + 1/\text{MOE Inhalation}}$

Table 3.4.2.6 Cancer dermal and inhalation exposure

Cancer dermal and inhalation exposure					
Dermal Units of exposure[1] (UE; µg/kg a.i. handled)	**Inhalation Units of exposure[1] (UE; µg/kg a.i. handled)**	**Amount of metofluthrin in cartridge (mg)**	**No. of cartridges used/day**	**Dermal Average Daily Dose[2] (ADD; mg/kg bw/day)[2]**	**Inhalation Average Daily Dose (ADD; mg/kg bw/day)[3]**
27270107	79200	16.5	1	5.54×10^{-3}	3.35×10^{-5}

1. Dermal and inhalation units of exposure: See Appendix I, Table 6
2. Dermal ADD = $\frac{\text{Dermal UE} \times \text{Amount a.i./cartridge} \times \text{No.of cartridges used/day} \times \text{conversion factors} \times \text{DA (48\%)}}{\text{BW (39 kg)}}$
3. Inhalation ADD = $\frac{\text{Inhalation UE} \times \text{Amount a.i./cartridge} \times \text{No.of cartridges used/day} \times \text{conversion}}{\text{BW (39 kg)}}$

For incidental dermal exposure to residues on the surface of a device during its use, incidental dermal exposure, expected from touching the device, was estimated using the passive dosimetry study which measured the total amount of residues accumulating on the device per hour.

Table 3.4.2.7 Incidental non cancer and cancer dermal exposure

Potentially transferable residue (µg/kg a.i. handled)	**Amount of metofluthrin in cartridge (mg)**	**No. of cartridges used/day**	**Exposure (mg/kg bw/day)[2]**	**MOE[3] (Target MOE = 300)**	**Average Daily Dose[4] (ADD; mg/kg bw/day)**
239333	16.5	1	1.01×10^{-4}	2 963 000	4.86×10^{-5}

1. Potentially transferable residue (see Appendix I, Table 6)
2. Exposure = $\frac{\text{Potentially transferable residue} \times \text{Amount a.i./cartridge} \times \text{No.of cartridges used/day} \times \text{conversion factor}}{\text{BW (39 kg)}}$
3. MOE = $\frac{\text{NOAEL (300 mg/kg bw/day)}}{\text{Exposure}}$
4. ADD = $\frac{\text{Dermal units of exposure} \times \text{Amount a.i./cartridge} \times \text{No.of cartridges used/day} \times \text{conversion factor} \times \text{DA (48\%)}}{\text{BW (39 kg)}}$

3.4.2.2.3 Children – Postapplication Exposure and Risk Assessment

Since the label does not prohibit the use by children, these individuals may be exposed to metofluthrin when wearing OFF! Clip On Mosquito Repellent while engaging in outdoor activities.

Similar to adults and youth, the exposure duration was considered intermediate as the clip on is used during the four months of mosquito season per year for 12 hours/day, according to the DEET insect repellent risk assessment from DEET joint venture (RRD2002-01 – *Personal insect repellents containing DEET (N,N-diethyl-m-toluamide and related compounds)*.

For dermal and inhalation exposure during the use of the device, a postapplication dermal exposure was estimated by coupling the units of exposure values from the passive dosimetry study (adjusted for children (0 - 6 years) based on an average surface area of 12650 cm^2 (NAFTA)) with the amount of product handled per day. Given the nature of clothing that is normally worn while engaging in outdoor activities, shorts and short sleeved shirt scenario were chosen from the USEPA Residential SOP (2009). For the part of the body that is covered a protection factor of 50% (according to NAFTA harmonization document used by USEPA for the addition of single layer permeable clothing when monitoring data are unavailable) was applied to the units of exposures (Appendix I, Table 6).

Although all the inhalation results in the passive dosimetry study for adults were non-detect, inhalation exposure was based on ½ LOQ.

Table 3.4.2.8 Non cancer dermal and inhalation exposure

Non cancer dermal and inhalation exposure								
Dermal units of exposure[1] (µg/kg a.i. handled)	**Inhalation units of exposure[1] (µg/kg a.i. handled)**	**Amount of metofluthrin in cartridge (mg)**	**No. of cartridges used/day**	**Dermal exposure (mg/kg bw/day)[2]**	**MOE[3] (target MOE = 300)**	**Inhalation exposure (mg/kg bw/day)[2]**	**MOE[3] (target MOE = 300)**	**Combined MOE**
16944114	42400	16.5	1	1.86×10^{-2}	16 000	4.66×10^{-5}	373000	25 000

1. Dermal and inhalation units of exposures: See Appendix I, Table 6

2. Dermal and Inhalation Exposures = $\frac{\text{UE} \times \text{Amount a.i./cartridge} \times \text{No.of cartridges used/day} \times \text{conversion factor}}{\text{BW (15 kg)}}$

3. MOE = $\frac{\text{NOAEL}}{\text{Exposure}}$

4. Combined MOE = $\frac{1}{1/\text{MOE dermal} + 1/\text{MOE Inhalation}}$

Table 3.4.2.9 Cancer dermal and inhalation exposure

Cancer dermal and inhalation exposure					
Dermal Units of exposure[1] (UE; µg/kg a.i. handled)	**Inhalation Units of exposure[1] (UE; µg/kg a.i. handled)**	**Amount of metofluthrin in cartridge (mg)**	**No. of cartridges used/day**	**Dermal average daily Dose[2] (ADD; mg/kg bw/day)[2]**	**Inhalation average daily dose (ADD; mg/kg bw/day)[3]**
16944114	42400	16.5	1	8.95×10^{-3}	4.66×10^{-5}

1. Dermal and inhalation units of exposure: See Appendix I, Table 6
2. Dermal ADD = $\frac{\text{Dermal UE} \times \text{Amount a.i./cartridge} \times \text{No.of cartridges used/day} \times \text{conversion factors} \times \text{DA}}{\text{BW (15 kg)}}$
3. Inhalation ADD = $\frac{\text{Inhalation UE} \times \text{Amount a.i./cartridge} \times \text{No.of cartridges used/day} \times \text{conversion}}{\text{BW (15 kg)}}$

For incidental dermal exposure to residues on the surface of a device during its use, incidental dermal exposure, expected from touching the device, was estimated using the passive dosimetry study which measured the total amount of residues accumulating on the device per hour.

Table 3.4.2.10 Incidental non cancer and cancer dermal exposure

Potentially transferable residue (µg/kg a.i. handled)	**Amount of metofluthrin in cartridge (mg)**	**No. of cartridges used/day**	**Exposure (mg/kg bw/day)[2]**	**MOE[3] (Target MOE = 300)**	**Average daily dose[4] (ADD; mg/kg bw/day)**
239333	16.5	1	2.63×10^{-4}	1 140 000	1.26×10^{-4}

1. Potentially transferable residue (see Appendix I, Table 6)
2. Exposure = $\frac{\text{Transferable residue} \times \text{Amount a.i./cartridge} \times \text{No.of cartridges used/day} \times \text{conversion factor}}{\text{BW (15 kg)}}$
3. MOE = $\frac{\text{NOAEL (300 mg/kg bw/day)}}{\text{Exposure}}$
4. ADD = $\frac{\text{Dermal units of exposure} \times \text{Amount a.i./cartridge} \times \text{No.of cartridges used/day} \times \text{conversion factor} \times \text{DA}}{\text{BW (15 kg)}}$

Incidental non-dietary oral exposure may occur when children touch the device, which has been running all day, with their hand then put their hand in their mouth and ingest the residues or accidentally put the actual device in their mouth.

Table 3.4.2.11 Incidental non cancer non-dietary oral exposure

Potentially transferable residue[1] (µg/kg a.i. handled)	**Amount of metofluthrin in cartridge (mg)**	**No. of cartridges used/day**	**Saliva removal efficiency (SRE; %)**	**Exposure[2] (mg/kg bw/day)[2]**	**MOE[3] (Target MOE = 300)**
239333	16.5	1	50	1.32×10^{-4}	114 000

1. Potentially transferable residue (see Appendix I, Table 6)
2. Exposure = $\frac{\text{Transferable residue} \times \text{SRE} \times \text{Amount a.i./cartridge} \times \text{No. cartridges/day} \times \text{conversion factor}}{\text{BW (15 kg)}}$
3. MOE = $\frac{\text{Oral NOAEL (15 mg/kg bw/day)}}{\text{Exposure}}$

For hand-to-mouth exposure the 90th percentile of hand residues was used from the passive dosimetry study after adjusting for children hand surface area (NAFTA). Since this is the amount that is found on the hand after a day of exposure, no transferable residue fraction is required.

Table 3.4.2.12 Hand-to-mouth noncancer exposure

Hand residue[1] (µg/kg a.i. handled)	Amount of metofluthrin in cartridge (mg)	No. of cartridges used/day	Fraction of hand surface area	Saliva removal efficiency (SRE; %)	Exposure[2] (mg/kg bw/day)	MOE[3] (Target MOE = 300)
12407040	16.5	1	20 / 904	50	1.50×10^{-4}	100 000

1. Hand residue (see Appendix I, Table 6) adjusted for child hand surface area
2. Exposure = $\frac{\text{Hand residue} \times \text{Amount a.i./cartridge} \times \text{No. of cartridges/day} \times \text{fraction of hand surface area} \times \text{SRE} \times \text{conversion factor}}{\text{BW (15 kg)}}$
3. MOE = $\frac{\text{Oral NOAEL (15 mg/kg bw/day)}}{\text{Exposure}}$

Table 3.4.2.13 Non cancer total incidental non-dietary oral exposure

Exposure from putting device in mouth (mg/kg bw/day)	Hand-to-mouth exposure (mg/kg bw/day)	Total exposure (mg/kg bw/day)	MOE (Target MOE = 300)
1.32×10^{-4}	1.50×10^{-4}	2.82×10^{-4}	53 000

3.4.2.3.1 Aggregate Non Cancer Assessment

For metofluthrin, the adverse effects of tremor and mortality were considered similar regardless of exposure routes. Thus it is appropriate to combine the route-specific margins of exposure (MOEs) into a single risk estimate. The route specific risk assessments have the same target MOE of 300, therefore, dermal, inhalation and oral MOEs were combined

Table 3.4.2.14 ADULT – Aggregate Non cancer Risk Assessment

DERMAL					INHALATION		Combined MOE
Applicator Exposure	Postapplication Exposure	Incidental Exposure	Total Exposure	MOE	Postapplication Exposure	MOE	
2.36×10^{-3}	9.37×10^{-3}	5.64×10^{-5}	1.18×10^{-2}	25 000	1.87×10^{-5}	932 000	25 000

Where: Combined MOE$= \frac{1}{\frac{1}{\text{MOE}_{\text{applicator + postapplication dermal + dermal incidental}}} + \frac{1}{\text{MOE}_{\text{Inhalation}}}}$

Table 3.4.2.15 YOUTH – Aggregate Non Cancer Risk Assessment

DERMAL				INHALATION		Combined MOE
Postapplication exposure	Incidental exposure	Total exposure	MOE	Postapplication exposure	MOE	
1.15 × 10-2	1.01×10^{-4}	1.16×10^{-2}	26 000	3.35×10^{-5}	519 000	25 000

Where: Combined MOE= $\frac{1}{\frac{1}{MOE_{\text{postapplication dermal + dermal incidental}}} + \frac{1}{MOE_{\text{Inhalation}}}}$

Table 3.4.2.16 CHILDREN – Aggregate Non Cancer Risk Assessment

DERMAL				INHALATION		INCIDENTAL ORAL				Combined MOE
Postapplication exposure	Incidental exposure	Total exposure	MOE	Postapplication exposure	MOE	Incidental exposure	Hand-to-mouth	Total exposure	MOE	
1.86×10^{-2}	2.63×10^{-4}	1.89×10^{-2}	16000	4.66×10^{-5}	373 000	1.32×10^{-4}	1.50×10^{-4}	2.82×10^{-4}	53 000	12 000

Where: Combined MOE= $\frac{1}{\frac{1}{MOE_{\text{postapplication dermal + dermal incidental}}} + \frac{1}{MOE_{\text{Inhalation}}} + \frac{1}{MOE_{\text{incidental oral ingestion}}}}$

3.4.2.3.2 Aggregate Cancer Assessment

To estimate the cancer risk, the lifetime average daily dose (LADD) must be determined. Exposure frequency is considered 15 days per year while the exposure duration is expected to be 63 years for adults, six years for youth and six years for children and a life expectancy of 75 years. Lifetime average daily dose will be multiplied by the q* value to determine the lifetime cancer risk (LCR).

$$LADD = \frac{ADD \times \text{Exposure frequency (day/year)} \times \text{Exposure duration}}{365 \text{ days/year} \times \text{Lifetime years}}$$

Table 3.4.2.17 Lifetime Cancer Risk

Age Category	Scenario	ADD	LADD	LCR
Adult	Dermal	5.66×10^{-3}	1.95×10^{-4}	2×10^{-6}
	Inhalation	1.87×10^{-5}	6.44×10^{-7}	7×10^{-9}
	Total			2×10^{-6}
Youth	Dermal	5.59×10^{-3}	1.84×10^{-5}	2×10^{-7}
	Inhalation	3.35×10^{-5}	1.10×10^{-7}	1×10^{-9}
	Total			2×10^{-7}
Children Children	Dermal	9.07×10^{-3}	2.98×10^{-5}	3×10^{-7}
	Inhalation	4.66×10^{-5}	1.53×10^{-7}	2×10^{-9}
	Ingestion	2.81×10^{-4}	9.26×10^{-7}	1×10^{-8}
	Total			3×10^{-7}
Lifetime				3×10^{-6}

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

4.1.1 Soil

Metofluthrin is not expected to persist in the terrestrial environment as it is subject to rapid aerobic biotransformation, with 50% dissipation time (DT_{50}) values of 2.9 to 3.4 days under laboratory conditions. Its major transformation products MFOA-D and TFPA are expected to further degrade in the soil.

Metofluthrin is not expected to be mobile in soil or to leach into groundwater, based on laboratory adsorption rates.

4.1.2 Water

Hydrolysis is not an important route of transformation. Under alkaline conditions, metofluthrin hydrolysed slowly (half-life of 33 days at pH 9) and was stable under neutral or acidic conditions.

4.1.3 Air

Based on the vapour pressure (1.96×10^{-3} Pa at 25ºC) and the Henry's law constant ($1/H = 1.754 \times 10^{3}$ at 25ºC), metofluthrin is expected to volatilize from moist soils or water surfaces. This is consistent with the use patterns proposed.

4.1.4 Biota

The estimated log K_{ow} values of metofluthrin (4.97-5.04) indicate this substance is likely to bioconcentrate or bioaccumulate; however, in a bioaccumulation study with carp, metofluthrin did not bioaccumulate significantly (bioconcentration factor = 110–120); and excretion was not further tested.

Data on the environmental fate and behaviour of metofluthrin are summarized in Appendix I, Table 7.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on nontarget species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental exposure concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (for example, protection at the community, population, or individual level). If the generation of quantitative data is not practical for a particular active ingredient/product, a qualitative assessment may be more appropriate.

The environmental risk assessment for metofluthrin was mainly qualitative as the proposed use patterns of the end-use product OFF! Clip On Mosquito Repellent will result in limited environmental exposure. The exposure cannot be quantified using standard scenarios, as the use of the product will not result in significant deposition of the active ingredient on soil, water or plants.

4.2.1 Risks to Terrestrial Organisms

Metofluthrin is practically non-toxic to birds and wild mammals. This active ingredient is, however, highly toxic to bees (Appendix I, Table 8). This is expected as metofluthrin is a pyrethroid insecticide.

Due to the limited use of OFF! Clip On Mosquito Repellent, the risk to nontarget terrestrial organisms will be negligible.

4.2.2 Risks to Aquatic Organisms

Metofluthrin is very highly toxic to aquatic invertebrates and fish (Appendix I, Table 8). However, due to the limited use of OFF! Clip On Mosquito Repellent, the risk to nontarget aquatic organisms will be negligible.

5.0 Value

5.1 Consideration of Benefits

OFF! Clip On Mosquito Repellent has value as it repels mosquitoes from the person wearing the device for up to 11 hours. Mosquitoes are an outdoor nuisance pest across all of Canada, especially in the morning and evening. Mosquito bites can cause discomfort and irritation, and can vector diseases such as West Nile Virus and other encephalitis-causing viruses. Protection from mosquito bites is important to prevent the possibility of contracting a mosquito-borne illness. In addition to health risks associated with mosquito bites, annoyance from mosquitoes can reduce the enjoyment of being outdoors and cause people to avoid outdoor activities when mosquito populations are heavy.

Alternative repellent products for protection from mosquitoes include skin-applied repellents (for example, sprays, wipes, and lotions) and area repellents (for example, candles, coils, and sprays). Many people do not like to use skin-applied repellents, and area repellents do not provide the same level of protection as a personal insect repellent. OFF! Clip On Mosquito Repellent is the first personal insect repellent product to be registered in Canada which is not skin-applied. As such, OFF! Clip On Mosquito Repellent has value as it provides an option to use a personal insect repellent that is not applied to the skin. Due to the method by which this product repels mosquitoes (in other words, a personal insect repellent using vaporized metofluthrin), OFF! Clip On Mosquito Repellent is only designed to work when the user is stationary and takes a few minutes to provide repellency after being turned on or when the user moves to a new location. Because metofluthrin is a repellent and not an insecticide, development of resistance to this product is not expected.

5.2 Acceptable Claims and Effectiveness Against Pests

Five studies were submitted for review. These studies included both field and laboratory studies and all were conducted on human volunteers. The reviewed studies were sufficient to demonstrate that OFF! Clip On Mosquito Repellent provided at least 95% mosquito repellency for up to 11 hours.

5.3 Non-Safety Adverse Effects

No nonsafety adverse effects are expected from use of OFF! Clip On Mosquito Repellent.

5.4 Supported Uses

A claim that OFF! Clip On Mosquito Repellent can repel mosquitoes from the wearer for up to 11 hours is supported.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy: in other words, persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, metofluthrin and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[4] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Metofluthrin does not meet all Track 1 criteria, and is not considered a Track 1 substance. See Appendix I, Table 9 for comparison with Track 1 criteria.

- Metofluthrin does not form any transformation products that meet all Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[5] The list is used as described in the PMRA Notice of Intent NOI2005-01[6] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02,[7] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusion:

- Technical grade Metofluthrin and the end-use product OFF! Clip On Mosquito Repellent do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette.*

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

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[4] DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

[5] *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette,* Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

[6] NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act*.

[7] DIR2006-02, *Formulants Policy and Implementation Guidance Document*.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for metofluthrin is adequate to define the majority of toxic effects that may result from exposure. In acute and chronic studies conducted with laboratory animals, the primary effect of metofluthrin was neurotoxicity characterized by clinical signs. There was also evidence of hepatotoxicity. Although there was no evidence of increased susceptibility of the young in the guideline toxicity studies submitted, residual uncertainty remains concerning this matter since literature studies indicate that young animals have pharmacodynamic and pharmacokinetic differences (such as the age-dependent maturation of key metabolic processes) that may lead to increased susceptibility of the young to pyrethroid toxicity. Although there was no evidence of carcinogenicity in mice following longer-term dosing, metofluthrin was carcinogenic in rats. The risk assessment protects against the toxic effects as noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Noncancer and cancer risk assessments for children, youth and adults were conducted. The noncancer risk assessments for children, youth and adults from the combined inhalation, dermal and incidental nondietary oral ingestion exposures were acceptable. The lifetime cancer risk for the general population was 3×10^{-6}, which exceeds the PMRA's level of concern. However, the passive dosimetry study and the dermal absorption study both had several major limitations resulting in considerable uncertainties in the units of exposure and dermal absorption values. Several conservatisms were also incorporated into the risk assessments (for example, 12 hours per day exposure duration and 15 times per year for an entire lifetime).

In light of the above, the OFF! Clip On Mosquito Repellent will be granted conditional registration pending a new passive dosimetry study and a new dermal absorption study. This risk assessment considered the exposure from the use of one device.

7.2 Environmental Risk

Metofluthrin is highly toxic to aquatic invertebrates, fish, and bees. However, based on the proposed use pattern as a personal insect repellent, adverse effects to these nontarget organisms are unlikely.

7.3 Value

OFF! Clip On Mosquito Repellent has value as a personal insect repellent as it repels mosquitoes from the person wearing the device for up to 11 hours. Mosquitoes are both an outdoor nuisance pest and a known vector of disease across all of Canada, especially in the morning and evening. Mosquito bites can also cause discomfort and irritation, and can vector diseases such as West Nile Virus and other encephalitis-causing viruses. Protection from mosquito bites is important to prevent the possibility of contracting a mosquito-borne illness. In addition to health risks associated with mosquito bites, annoyance from mosquitoes can reduce the enjoyment of being outdoors and cause people to avoid outdoor activities when mosquito populations are heavy.

8.0 Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, has granted conditional registration for the sale and use of SumiOne Technical Grade and OFF! Clip On Mosquito Repellent, containing the technical grade active ingredient metofluthrin, as a personal mosquito repellent.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

Although the risks and value have been found acceptable when all risk-reduction measures are followed, as a condition of these registrations, additional scientific information is being requested. For more details, refer to the Section 12 Notice associated with these conditional registrations. The applicant will be required to submit this information within the time frames indicated below.

NOTE: The PMRA will publish a consultation document at the time when there is a proposed decision on applications to convert these conditional registrations to full registrations or on applications to renew the conditional registrations, whichever occurs first.

Human Health

To further confirm the units of exposure and dermal absorption value used in the risk assessment, conditional registration of the OFF! Clip On Mosquito Repellent can be supported pending the submission of the following:

- New passive dosimetry study to estimate the amount of metofluthrin deposited on the surface of the skin and the amount of the chemical available for inhalation through the use of appropriate trapping devices for both adults and children. The study must be done according to acceptable guidelines.

- New *In vivo* dermal absorption study to estimate the dermal absorption of metofluthrin with longer monitoring periods to better determine the fate of the skin bound residues. The study must be done according to acceptable guidelines.

List of Abbreviations

1/H	Henry's law constant
↑	increase
↓	decrease
<	less than
>	greater than
≥	greater than or equal to
♀	female
♂	male
µg	micrograms
µL	microlitre
a.i.	active ingredient
abs	absolute
ADD	average daily dose
ADI	acceptable daily intake
ads.	adsorption
ARfD	acute reference dose
AUC	area-under-the-curve
BAF	Bioaccumulation factor
BCF	Bioconcentration factor
BrdU	bromodeoxyuridine
bw or BW	body weight
bwg	body-weight gain
CAS	Chemical Abstracts Service
CBI	confidential business information
CD	Charles Darwin
cm^2	centimetre squared
CYP	Cytochrome P450
d	day(s)
DA	dermal absorption
DACO	Data Code
DEET	N,N-diethyl-m-toluamide
DIR	Regulatory Directive
DSS	dioctyl sodium sulfosuccinate
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
dw	dry weight
EC_{50}	effective concentration on 50% of the population
EEC	estimated environmental concentration
EPA	Environmental Protection Agency
F_1	first generation
fc	food consumption
FOB	functional observation battery
g	gram
GC-MS	gas chromatography / mass spectrometry
GD	gestation day

GGT	gamma glutamyltransferase
GJIC	gap junction intercellular communication
GLP	Good Laboratory Practice
GPMT	Guinea Pig Maximization text
GSH	Glutathione
GST	glutathione S-transferase
ID	identification
IPA	isopropyl alcohol
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
L	litre
LC_{50}	lethal concentration 50%
LADD	lifetime average daily dose
LCR	lifetime cancer risk
LD	lactation day
LD_{50}	lethal dose 50%
LDH	lactate dehydrogenase
LOAEC	lowest observed adverse effect concentration
LOAEL	lowest observed adverse effect level
LOQ	limit of quantitation
m^3	cubed metre(s)
mg	milligram
mL	millilitre
MAS	maximum average score
MFFO	phototransformation product
MFOA	phototransformation product
min	minute
MIS	maximum irritation score
MOA	Mode of action
MOE	margin of exposure
MRID	United States Master Record Identification Number
mRNA	messenger ribonucleic acid
N/A	not applicable
NAFTA	North American Free Trade Agreement
nm	nanometre
No.	number
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NOI	Notice of Intent
NZW	New Zealand white
OVS	OSHA Versatile Sampler
P	parental generation
Pa	Pascal(s)

pH	measure of the acidity or basicity of an aqueous solution
pK_a	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	postnatal day
P_{ow}	n-Octanol-water partition coefficient
ppm	parts per million
q_1*	cancer potency factor
rel	relative
RRD	Re-Evaluation Decision document
SER	smooth endoplasmic reticulum
SOP	standard operating procedure
SRE	Saliva Removal Efficiency
$t_{1/2}$	half-life
T_{max}	time to maximum concentration
TSMP	Toxic Substances Management Policy
UDPGT	Uridine Diphosphate Glucuronyltransferase
UE	Units of exposure
UF_{DB}	database uncertainty factor
USEPA	United States Environmental Protection Agency
UV	ultraviolet
wt(s)	weight(s)

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ	References
Fish	None	metofluthrin	GC-MS	0.002 mg/kg	1504797 1836734
Soil	None	metofluthrin	GC-MS	0.01 mg/kg	1836732 1836733

Table 2 Toxicity Profile of OFF! Clip On Mosquito Repellent

Study Type/Animal/PMRA #	Study Results
Oral Sprague-Dawley rats PMRA 1504744	LD_{50}>2000 mg/kg bw Low Acute Toxicity
Dermal Sprague-Dawley rats PMRA 1504747	LD_{50}>2000 mg/kg bw Low Acute Toxicity
Inhalation (nose-only) Sprague-Dawley rats PMRA 1504749	LC_{50} =0.862- 2.00 mg/L air (gravimetrically determined) Slight Acute Toxicity
Eye Irritation NZW rabbits PMRA 1504750	MAS = 0.23 (nonirrigated) MAS = 0.08 (irrigated) MIS = 0.7 at 24 hours (both groups) Minimally Irritating
Dermal Irritation NZW rabbits PMRA 1504752	MAS = 0 MIS = 0 Nonirritating
Dermal Sensitization (GPMT) Hartley guinea pigs PMRA 1504754	 Not a skin sensitizer

Table 3 Toxicity Profile of Phototransformation Product (MFFO)

Study Type/Animal/PMRA #	Study Results
Oral Phototransformation Product (MFFO) Sprague-Dawley rats PMRA 1504742	LD_{50}>2000 mg/kg bw Low Acute Toxicity
Dermal Phototransformation Product (MFFO) Sprague-Dawley rats PMRA 1504745	LD_{50}>2000 mg/kg bw Low Acute Toxicity
Dermal Irritation Phototransformation Product (MFFO) NZW rabbits PMRA 1504753	MAS = 0 MIS = 0 Nonirritating
Dermal Sensitization Phototransformation Product (MFFO) Hartley guinea pigs PMRA1504755	 Not a skin sensitizer

Table 4 Toxicity Profile of Technical Metofluthrin

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted). Effects seen above the LOAEL(s) have not been reported in this table for most studies for reasons of brevity.)

Study Type/Animal/PMRA #	Study Results
Metabolism Sprague-Dawley rats PMRA 1504789 PMRA 1504790 PMRA 1504791 PMRA 1504792 PMRA 1504793	**Absorption** Overall recoveries of radioactivity from all groups were high (greater than 96% of the administered dose). Absorption was rapid with radioactivity detected in plasma 30 minutes post-dosing. Absorption was 57-68 % for the [carbonyl-^{14}C]S-1264RTZ label, 42-79% for the [carbonyl-^{14}C]S-1264RTE label, and 60-70 % for the [methoxymethylbenzyl-α-^{14}C]S-1264RTZ label. The time to maximum concentration (T_{max}) in plasma was 3.3-7 hours. The half-life in plasma ranged from 52-138 hours regardless of sex, dose or label. The area-under-the-curve (AUC) was slightly higher for females suggesting a higher systemic exposure. The AUC from low to high dosing was proportional to dose; thus, absorption was not saturated. **Distribution** The maximum time for tissue concentration was 2-6 hours for almost all tissues. The liver followed by the kidney contained the highest concentration of radioactivity. For all tissues, the levels decreased in a time-dependent fashion such that only 0.2% of the administered dose remained in the tissues by 168 hours. For the rats administered the [methoxymethylbenzyl-α-^{14}C]S-1264RTZ radiolabel, blood cells and spleen appeared to show slightly slower decrease; however, radioactivity concentration as a percentage of the administered dose was 0 at the 168 hour time point. The repeated administration studies did not reveal any evidence of bioaccumulation. **Excretion** There were slight differences in excretion depending on the label. Excretion using the [carbonyl-^{14}C]S-1264RTZ or [carbonyl-^{14}C]S-1264RTE label was 29-57% of administered radioactivity in the urine, and 20-52% of administered radioactivity in the feces. In bile-cannulated rats, 31-40% radioactivity was detected in the bile for the [carbonyl-^{14}C]S-1264RTZ radiolabel and 27-55% for the carbonyl-^{14}C]S-1264RTE radiolabel. Excretion of the [methoxymethylbenzyl-α-^{14}C]S-1264RTZ radiolabel was 60-70% in urine and 26-36% in feces. Most of the administered dose was excreted by 24 hours. **Metabolism** The test material was extensively metabolized with a total of 46 metabolites identified, accounting for 72-92% of the administered dose. The parent compound was detected in feces but not urine. In bile-cannulated rats, the parent compound was detected in feces but not urine or bile. In urine, the major metabolite following administration of [methoxymethylbenzyl-α-^{14}C]S-1264RTZ was X1 (14-17% AD) and X2 (26-35% AD) which was observed in the single administration but not in the repeated dose studies. A major unknown metabolite (KUK1) was identified in the kidney of low and high-dose females (33-34% AD) but only in minor amounts in males (2-3%AD). The primary fecal metabolite was Ac16, accounting for 11-14% of the administered dose in the [carbonyl-^{14}C]S-1264RTE group. Based upon the isolated metabolites, the major pathways of metabolism were cleavage of the ester linkage, oxidation of the methyl groups on the benzyl moiety to form alcohol, aldehyde and carboxylic acid metabolites, reduction of the double bond in the acid moiety of the molecule, and formation of glutathione and sulphate adducts.
Oral Sprague-Dawley rats	LD_{50}>2000 mg/kg bw Low Acute Toxicity

Study Type/Animal/PMRA #	Study Results
PMRA 1504744	
Dermal Sprague-Dawley rats PMRA 1504747	LD_{50}>2000 mg/kg bw Low Acute Toxicity
Inhalation (nose-only) Sprague-Dawley rats PMRA 1504749	LC_{50} =0.862- 2.00 mg/L air (gravimetrically determined) Slight Acute Toxicity
Eye Irritation NZW rabbits PMRA 1504750	MAS = 0.23 (non-irrigated) MAS = 0.08 (irrigated) MIS = 0.7 at 24 hours (both groups) Minimally Irritating
Dermal Irritation NZW rabbits PMRA 1504752	MAS = 0 MIS = 0 Nonirritating
Dermal Sensitization (GPMT) Hartley guinea pigs PMRA 1504754	 Not a skin sensitizer
Oral S-1264 Sprague-Dawley rats PMRA 1504743	LD_{50}>2000 mg/kg bw Low Acute Toxicity
Dermal S-1264 Sprague-Dawley rats PMRA 1504747	LD_{50}>2000 mg/kg bw Low Acute Toxicity
Inhalation (nose-only) S-1264 Sprague-Dawley rats PMRA 1504749	LC_{50}>2.00 mg/L air (gravimetrically determined) Clinical signs: tremors, hypersensitivity, ataxic gait, tiptoe gait, clonic convulsion Slight Acute Toxicity
Eye Irritation S-1264 NZW rabbits PMRA 1504751	MAS = 0 (nonirrigated) MAS = 0 (irrigated) MIS = 0 (both groups) Non irritating
Dermal Irritation S-1264 NZW rabbits PMRA 1504751	MAS = 0.9 MIS = 1.6 (1 hr) Slightly irritating
Dermal Sensitization (GPMT)	

Study Type/Animal/PMRA #	Study Results
S-1264 Hartley guinea pigs PMRA 1504756	 Not a skin sensitizer
90-Day Oral Toxicity (diet) CD-1 mice PMRA 1504759	NOAEL= 357/439 mg/kg bw/day (♂/♀) LOAEL = 487/587 mg/kg bw/day Effects at LOAEL: ↑ hepatocellular hypertrophy, ↑liver wt, liver degeneration/necrosis,↑ Kupffer cells; ↑phospholipids, ↑ triglycerides, ↑cholesterol (♀)
28-Day Oral Toxicity (diet) Sprague-Dawley rats PMRA 1504762	NOAEL = 29 mg/kg bw/day (♂) LOAEL = 96 mg/kg bw/day Effects at LOAEL: ↓ bw [day 8],↓ bwg [week 1], ↑cholesterol, ↑phospholipids,↑ rel liver wts, ↑ hepatocellular hypertrophy (slight/mild) NOAEL = 95 mg/kg bw/day **(**♀**)** LOAEL = 273 mg/kg bw/day Effects at LOAEL: tremors, ↑ LDH, dark liver**,** ↑liver wt, ↑ GGT, ↑ cholesterol, ↑ phospholipids, mortality (1 animal on day 4) Recovery Group: ↑ liver wt (both sexes)
90-Day Oral Toxicity (diet) Wistar rats PMRA 1504758	NOAEL = 21/22 mg/kg bw/day (♂/♀) LOAEL = 70/73 mg/kg bw/day Effects at LOAEL: ↑ hepatocellular basophilia and hypertrophy**,** ↑liver wt, ↑cholesterol, ↑phospholipids; ↑total protein, ↑leukocytes in urine, enlarged liver (♂)
6-Month Oral Toxicity (diet) Sprague-Dawley rats PMRA 1504768	NOAEL = 16/19 mg/kg bw/day (♂/♀) LOAEL = 54/65 mg/kg bw/day Effects at LOAEL: enlarged liver, hepatocellular hypertrophy (slight-mild), ↑hepatic microvesicular steatosis (slight-mild); ↑ albumin, ↑total cholesterol, ↑phospholipids, dark liver (♂);↓ bilirubin (♀)
90-Day Dermal Toxicity Sprague-Dawley rats PMRA 1504763	NOAEL for systemic toxicity = 300 mg/kg bw/day LOAEL for systemic toxicity = 1000 mg/kg bw/day Effects at LOAEL: mortality (2 ♀) – one displayed tremors and salivation and both were found dead on day 3; ↑ squamous cell hyperplasia (integument) NOAEL for dermal irritation = 10 mg/kg bw/day (based on combined results of this study as well as PMRA 1504757) LOAEL for dermal irritation = 30 mg/kg bw/day Effects at LOAEL: hyperactivity and vocalization were observed for the first 4 days only, and only prior to removal of test substance from the skin at the end of the 6-hr contact period.
Dose finding study for clinical signs by single dermal administration of S-1264 Sprague-Dawley rats PMRA 1504757	No clinical signs were observed up to/including 30 mg/kg bw using the same conditions of application as in the 90-day dermal toxicity study (PMRA 150763). This study report also mentions another study which was performed prior to this dose-range study in which 12 ♀/group received either 10, or 30 mg/kg bw as a single dermal dose with occlusion for a 6hr contact period. Animals dosed at 30 mg/kg bw displayed vocalization (1♀) and hyperactivity (2 other♀) within 30 minutes of dosing as well as after 3-5 hours. No clinical findings were observed at 10 mg/kg bw.
28-Day Inhalation (nose-only) Toxicity Sprague-Dawley rats	NOAEC = 0.100 mg/L air (equivalent to 17 mg/kg bw/day) LOAEC = 0.200 mg/L air Effects at LOAEC: mortality, tremor, hypersensitivity, ataxic gait, tiptoe gait, lateral position, clonic convulsion, hypothermia

Study Type/Animal/PMRA #	Study Results
PMRA 1504764	
28-Day Inhalation (nose-only) Toxicity Sprague-Dawley rats PMRA 1504765	NOAEC = 0.100 mg/L air (equivalent to 17.4 mg/kg bw/day) LOAEC = 0.200 mg/L Effects at LOAEC: mortality, ↑ clinical signs such as tremors, tiptoe gait, lateral position, clonic convulsion; ↑ liver wt, centrilobular hypertrophy (1/6 ♂); slight ↓ bw (♀)
90-day inhalation PMRA 1836724	Waiver request granted based on availability of a 28-day inhalation study and lack of an increase in toxicity with increased duration of dosing in the rest of the database. The proposed use scenario would result in short to intermediate term intermittent inhalation exposure. In light of this, the 28-day inhalation study was deemed sufficient to support the proposed use.
90-Day Oral Toxicity (capsule) Beagle dog PMRA 1504760	NOAEL = 10 mg/kg bw/day (♂) LOAEL = 30 mg/kg bw/day (♂) Effects at LOAEL: ↑ vomiting [2-6 hours post-dosing] (♂) NOAEL = 30 mg/kg bw/day(♀) LOAEL = 100 mg/kg bw/day(♀) Effects at LOAEL: tremors, ↑salivation, ↓ thymus wt,; ↑ vomiting,↑ thymus wt, ↑ pituitary wt Tremors began within 2-6 hours of dosing, beginning week 4 in ♂ and day 10 in ♀] Recovery: only finding was vomitus on one occasion in each of one high dose ♂ & ♀
12-Month Oral Toxicity (gavage) Beagle dogs PMRA 1504761	NOAEL = 10 mg/kg bw/day LOAEL = 30 mg/kg bw/day Effects at LOAEL: ↑ tremors (sporadic); ↑ vomiting, ↓ reticulocyte count (♂); ↓ leukocyte / eosinophil / neutrophil counts, ↓ uterus wt, ↑ submaxillary gland wt (♀) Tremors began 2-4 hours following dosing; transient and occurring later in the study in mid-dose animals (≥ week 14); occurring early (after a few doses) in high dose animals]
78-Week Oncogenicity (diet) CD-1 mice PMRA 1504775	NOAEL = 116/155 mg/kg bw/day (♂/♀) LOAEL = 209/277 mg/kg bw/day Effects at LOAEL:↓bwg , lung congestion; ↑ lung discolouration(♂); ↑ liver and heart weights (♀) No evidence of carcinogenicity
104-Week Chronic Toxicity/ Oncogenicity (diet) Wistar rats PMRA 1504698 PMRA 1504776 PMRA 1512273 PMRA 1512275	NOAEL = 8.2/10.1 mg/kg bw/day (♂/♀) LOAEL = 38.1/47.4 mg/kg bw/day Effects at LOAEL: ↓ bwg, ↑ liver nodules; ↓ bw, ↑ cholesterol, ↑ albumin, ↑ triglycerides, ↑ protein, ↑ phospholipids, ↑ GGT, ↑rel liver wts (week 52 only), ↑ liver mixed cell foci (♂); ↑ rel. liver wts (termination), ↑ hepatocellular hypertrophy, ↑ liver clear cell foci, ↑ lung foci (♀) Evidence of carcinogenicity (increased incidence of combined liver adenoma/carcinoma in both sexes)
Developmental Toxicity (gavage) Sprague-Dawley rats PMRA 1504783	<u>Maternal Toxicity:</u> NOAEL = 15 mg/kg bw/day LOAEL = 30 mg/kg bw/day Effects at LOAEL: tremors (2-3 hours post-dosing; GD 10-19) <u>Developmental Toxicity:</u> NOAEL = 30 mg/kg bw/day

Study Type/Animal/PMRA #	Study Results
	LOAEL = not established as no effects were observed No evidence of teratogenicity or sensitivity of the young
Developmental Toxicity (gavage) NZW rabbits PMRA 1504782	Maternal Toxicity: NOAEL = 25 mg/kg bw/day LOAEL = 125 mg/kg bw/day Effects at LOAEL: mortality (1 at GD 23); also mortality (1 at GD 13) at next highest dose (250 mg/kg bw/day) Developmental Toxicity: NOAEL = 250 mg/kg bw/day LOAEL = not established as no effects were observed No evidence of teratogenicity or sensitivity of the young
Reproductive Toxicity Study (diet) Sprague-Dawley rats PMRA 1836727 PMRA 1836728 PMRA 1836729 PMRA 1836740	A NOAEL and LOAEL were not established as this was a dose range finding study. Parental Toxicity: Effects noted at 147/150 mg/kg bw/day: ↑ liver wts; tremors/twitches (lactation), excessive salivation (gestation), dehydration (premating/lactation) (♀) Reproductive Toxicity: Effects noted at 292/328 mg/kg bw/day: slight ↓implantations/dam, ↓live births, ↑ stillborn pups Offspring Toxicity: Effects noted at 150 mg/kg bw/day: ↓bw /bwg (PND7-21), ↓lactation index, ↑clinical signs (cold to touch, not nursing, not nesting, dehydrated, tremors, twitches – post-weaning)
One-generation Reproduction Study (gavage) Sprague-Dawley rats PMRA 1504781	A NOAEL and LOAEL were not established as this study was considered supplemental. Maternal Toxicity: Effects at 15 mg/kg bw/day: mortality during lactation (1 at 15 and 1 at 30 mg/kg bw/day; one death occurred on LD 0, and the other occurred on LD 2) Reproductive Toxicity: No adverse findings Offspring Toxicity: No adverse findings
Fertility and Early Embryonic Development to Implantation (gavage) Sprague-Dawley rats PMRA 1504794	A NOAEL and LOAEL were not established as this study was considered supplemental. Parental Toxicity: Effects at 40 mg/kg bw/day: ↑mortality (pre-mating, gestation), ↑tremor and salivation (pre-mating, gestation), ↓ fc, ↓ bwg (week one only) (♀) Reproductive Toxicity: No adverse findings. Fetal Toxicity: No adverse findings.
2-generation Reproductive Toxicity Study (diet)	Parental Toxicity: NOAEL = 15/16 mg/kg bw/day (♂/♀)

Study Type/Animal/PMRA #	Study Results
Sprague-Dawley rats PMRA 1504770 PMRA 1512790	LOAEL = 70/77 mg/kg bw/day Effects at LOAEL: ↑ soft/liquid feces (P/F_1 ♂), ↑ slight salivation (P gestation and lactation); ↑ body tremors and twitches (F_1 ♀ lactation); ↑ chromorhinorrhea (F_1 ♀ lactation); ↓ bw and bwg (F_1♀ initial and final premating); ↓ bw (F_1 ♀ gestation and lactation with partial recovery); ↑ liver wts (P♂, F_1 ♀) with ↑ hepatocellular hypertrophy (♂) <u>Reproductive Toxicity:</u> NOAEL = 70/77 mg/kg bw/day (♂/♀) LOAEL = 126/140 mg/kg bw/day Effects at LOAEL: ↓ follicle counts (F_1) <u>Offspring Toxicity:</u> NOAEL = 16 mg/kg bw/day LOAEL = 77 mg/kg bw/day Effects at LOAEL: delayed preputial separation No evidence of sensitivity of the young
Bacterial Reverse Gene Mutation S-1264 PMRA 1504785	Negative
Bacterial Reverse Gene Mutation S-1264ZR PMRA 1504786	Negative
Chromosome Aberrations (*in vitro*) S-1264 Chinese Hamster Lung V79 Fibroblast PMRA 1504787	Negative
Micronucleus Assay (*in vivo*) S-1264 CD-1 mice PMRA 1504788	Negative
Bacterial Reverse Gene Mutation MFFO PMRA 1504784	Negative
Acute Neurotoxicity (gavage) Sprague-Dawley rats	NOAEL = 50 mg/kg bw LOAEL = 100 mg/kg bw Effects at LOAEL: ↑ motor activity (day of dosing), ↑mortality, ↑tremors/twitches; ↑tachypnea, FOB alterations (♂)

Study Type/Animal/PMRA #	Study Results
PMRA 1504778 PMRA 1836731	Evidence of neurotoxicity
13-Week Neurotoxicity (diet) Sprague-Dawley rats PMRA 1504780	NOAEL= 60/69 mg/kg bw/day (♂/♀) LOAEL = 178/206 mg/kg bw/day Effects at LOAEL: ↓bw/bwg, ↓ fc; ↑soft/liquid/scant feces (♂); ↑tremors/twitches, mortality (♀) Evidence of neurotoxicity
Pilot Study for Mode of Action of S-1264 for Liver Promotion in Rats (diet) Wistar rats PMRA 1504772	Toxicity to the liver was assessed by gross and microscopic examinations: <u>Metofluthrin:</u> ≥ 450 ppm: ↑ liver wts, enlarged liver (♂). ≥ 1800 ppm: slight hepatocellular hypertrophy; ↑ liver wts, enlarged liver(♀). 2700 ppm: dilatation and/or proliferation of smooth endoplasmic reticulum in hepatocytes (♂ - slight; ♀ - mild) <u>Phenobarbital:</u> 1000 ppm: ↑ liver weights, enlarged liver, moderate to severe hepatocellular hypertrophy, dilatation and/or proliferation of smooth endoplasmic reticulum in hepatocytes (♂ - mild; ♀ - moderate). Cell proliferation using BrdU uptake in the liver: <u>Metofluthrin:</u> Observed in ♂ at 1800 and 2700 ppm after 1- week treatment but not at 2700 ppm after 2- week treatment. Not observed in ♀ after 2- or 4-week treatment. <u>Phenobarbital:</u> Demonstrated in ♂ that were treated for 1 week. Not demonstrated in ♀. Control data in this study were highly variable. Total microsomal protein levels and P450 protein levels: <u>Metofluthrin:</u> No ↑ protein levels in either sex at any dose level. <u>Phenobarbital:</u> ↑ total microsomal protein levels in ♂ and ↑ total P450 levels in both sexes. mRNA protein levels and CYP protein levels: <u>Metofluthrin:</u> ≥ 450 ppm: ↑CYP2B1/B2 mRNA (♂) ≥ 1800 ppm: ↑CYP2B1/B2 mRNA (slight), ↑CYP2B protein levels (♀) 2700 ppm: ↑CYP2B protein levels (slight) (♂); ↑CYP3A1 mRNA, ↑CYP3A protein levels (slight) (♀) <u>Phenobarbital:</u> ↑CYP2B1/B2, CYP3A1 and CYP3A2 mRNA levels, ↑CYP2B and CYP3A protein levels.
Study for Mode of Action of S-1264 for Liver Promotion in Rats (diet) Wistar Rats PMRA 1504773	Toxicity to the liver was assessed by gross and microscopic examinations: <u>Metofluthrin:</u> ≥ 1800 ppm: ↑rel liver wt, enlarged liver, ↑ hepatocellular hypertrophy; dark liver (♂); ↓bw/bwg, ↓ fc (♀) 3600 ppm: mortality, tremors, ↓ hepatic vacuolation, dilatation and/or proliferation of sER in hepatocytes; ↓bw/bwg, ↓ fc(♂); dark liver (♀) Recovery: Only finding was enlarged liver in 2/5 ♂ at 1800 ppm, as well as in 2/5 ♂ and 2/5 ♀ at 3600 ppm <u>Phenobarbital (1000 ppm – dose used for all assessments)</u>: ↓ bwg during recovery, ↑ liver wt, enlarged and/or dark liver, ↑ hepatocellular hypertrophy, dilatation and/or proliferation of sER in hepatocytes; ↑ early bwg (♂).

Study Type/Animal/PMRA #	Study Results
	Cell proliferation using BrdU uptake in the liver: Metofluthrin: ↑cell proliferation in ♂ at 900 and 1800 ppm, but not at 3600 ppm; ↑cell proliferation in ♀ at 1800 and 3600 ppm. Phenobarbital: ↑cell proliferation was demonstrated in both sexes. Total microsomal protein levels and P450 protein levels: Metofluthrin: No difference in either sex at any dose level Phenobarbital: ↑ total P450 levels in both sexes; ↑microsomal protein levels (♂) mRNA and CYP protein levels: Metofluthrin: ≥900 ppm: ↑ CYP2B1/B2 mRNA(♀) ≥1800 ppm: ↑ CYP2B1/B2 mRNA (♂);↑CYP3A1 mRNA (♀) 3600 ppm: ↑ CYP2B protein levels; ↑CYP3A1 mRNA (♂) Phenobarbital: ↑ CYP2B1/B2, CYP3A1 and CYP3A2 mRNA levels and CYP2B protein levels. Findings were reversible upon cessation of treatment.
The 2nd Study for Mode of Action of S-1264 for Liver Promotion in Rats (diet) Wistar Rats PMRA 1504774	Metofluthrin: ≥1800 ppm: ↑ liver wt, hepatocellular hypertrophy, ↓ hepatocellular vacuolation, dark and/or enlarged liver (♂) 3600 ppm: tremors, ↓bwg early in treatment period; mortality, ↑ liver wt, dark and/or enlarged liver, hepatocellular hypertrophy and ↓ hepatocellular vacuolation (♀) Phenobarbital: ↑ early bwg, ↑ liver wts, enlarged and/or dark liver,↑ hepatocellular hypertrophy; ↑ liver wt after recovery (♂); ↓ bwg during recovery, ↓ hepatocellular vacuolation (♀) GJIC capacity: Metofluthrin: ≥1800 ppm: ↓ distance of dye transfer Phenobarbital: ↓ distance of dye transfer Oxidative stress: Metofluthrin: No↑ in lipid peroxidation levels or apoptosis ≥900 ppm: ↑ total GSH; ↑reduced GSH (♂) ≥1800 ppm: ↑ reduced GSH (♀) Phenobarbital: ↑ total GSH, ↓ apoptosis (♂); ↑ lipid peroxidation levels, ↑ reduced GSH (♀) Recovery: Metofluthrin: Findings were reversible on cessation of treatment with the exception of ↓ bwg in 3600 ppm (♀).
Study for Mode of Action of S-1264 for Liver Tumor Promotion in Rats (In vitro effect of S-1264 on cytochrome P450 activity and mRNA level)	7-pentoxyresorufin *O*-dependentylase enzyme measurements: Metofluthrin: ↑in rat and human hepatocytes but not in mouse. Phenobarbital: ↑ in rat, human, and mouse hepatocytes

Study Type/Animal/PMRA #	Study Results
Hepatocytes derived from human, rat, mouse PMRA 1504766	CYP2B mRNA level measurements: Metofluthrin: ↑ in rat and human hepatocytes but not in mouse Phenobarbital: ↑ in rat, human and mouse hepatocytes
Gene Expression Profiling Analysis of Early Phase of Treatment in the Liver from S-1264 Treated Rats Frozen livers obtained from MOA study (PMRA#1504773) PMRA 1504770	Metofluthrin-treated liver (1800 ppm): 25 probe sets were up-regulated and 10 probe sets were down-regulated. Sodium phenobarbital group (1000 ppm): 85 probe sets were up-regulated and 14 probe sets were down-regulated. Of the 25 probe sets up-regulated in the metofluthrin group, 21 (84%) were also up-regulated in the sodium phenobarbital group. Of the 10 probes down-regulated in the S-1264 group, 4 (40%) were also down-regulated in the sodium phenobarbital group. Most up-regulated genes following treatment with S-1264 were GSTs, CYPs, and UDPGTs (metabolic), which were also the genes up-regulated with sodium phenobarbital. Conclusion: Metofluthrin was similar to sodium phenobarbital in gene up-regulation, although the number of genes altered by metofluthrin was less than that of sodium phenobarbital.

Table 5 Toxicology Endpoints for Use in Health Risk Assessment for Metofluthrin

Exposure Scenario	Study	Point of Departure and Endpoint	Target MOE[1]
Acute dietary	Not required as there are no food uses.		
Repeated dietary	Not required as there are no food uses.		
Short-term to Intermediate-term dermal	Rat 90-day dermal	NOAEL: 300 mg/kg bw/day; based on mortality, clinical signs and an increased incidence of squamous cell hyperplasia (skin)	300
Short-term to Intermediate-term inhalation	Rat 28-day inhalation	NOAEC: 0.1 mg/L (equivalent to 17.4 mg/kg bw/day); based on mortality, clinical signs, liver effects, decreased body weight	300
Non-dietary oral ingestion (short-term)	Rat developmental toxicity	NOAEL: 15 mg/kg bw/day; based on tremors in dams post-dosing	300
Cancer	Rat chronic/oncogenicity	q_1*= 1.13x10-2 (mg/kg bw/day) $^{-1}$ based on liver adenomas and carcinomas in females	

[1] MOE refers to a target MOE for occupational and residential assessments

Table 6 Results of Passive Dosimetry Study

	Units of Exposure (µg / kg a.i. handled)								
Replicate No.	**Patch ID # 1 representing lower leg (2370 cm^2)**	**Patch ID # 2, 3 and 7 representing upper leg and thighs (3540 cm^2)**	**Patch ID # 4 and 5 representing trunk (6590 cm^2)**	**Patch ID # 6 representing Lower arm/fore arm (1173 cm^2)**	**Upper arm (1433 cm^2) extrapolated from Patch ID 5**	**Hands (904 cm^2) extrapolated from Patch ID 3**	**Feet (1225 cm^2) extrapolated from Patch ID 1**	**Head and neck (1205 cm^2) extrapolated from Patch ID 5**	**Total Exposure (18440 cm^2)**
1	3384000	5056000	9416000	1680000	2040000	1289600	1744000	1712000	26321600
2	3384000	26256000	9416000	1680000	2040000	7955200	1744000	1712000	54187200
3	3384000	25944000	9416000	1680000	2040000	1.4E+07	1744000	1712000	59440000
90th Percentile	3384000	26193600	9416000	1680000	2040000	12407040	1744000	1712000	58389440
Uncovered	3384000			1680000		12407040	1744000	1712000	
Covered (50% protection factor)		13096800	4708000		1020000				

Table 7 Fate and Behaviour in the Environment

Study	Test substance	Value	Remarks	Reference
Hydrolysis	metofluthrin	$t_{½}$ at 25ºC and pH 9: 33 days Stable at pH 4 and 7	Is not an important route of transformation	1504798
Biotransformation in aerobic soil	metofluthrin	Parent DT_{50}: 2.9 – 3.4 days Transformation products MFOA-D DT_{50}: 13.4-18.2 days TFPA DT_{50}: 6.2-76.9 days	Is an important route of transformation of the parent compound	1504799 1504800 1504802
Adsorption / desorption in soil	metofluthrin	Ads. K_{OC}: 2729 - 11855	Slightly mobile to immobile	1504804
Bioaccumulation	metofluthrin	Bioconcentration factor: 110-120	Does not bioaccumulate significantly	1504797

Table 8 Toxicity to Non-Target Organisms

Organism	Study type	Test substance	Endpoint value	Degree of toxicity [a]	Reference (PMRA#)
Terrestrial Organisms					
Bee (*Apis mellifera*)	Acute Contact (48-hour)	metofluthrin	LD_{50} = 0.016 µg a.i./bee	Highly toxic	1630829
Bobwhite quail (*Colinus virginianus*)	Acute	metofluthrin	LD_{50} >2250 mg a.i./kg bw NOEL (sub-lethal effects) = 486 mg a.i./kg bw	Practically non-toxic	1504814
	Dietary (5-day)	metofluthrin	LC_{50} > 5760 mg a.i./kg dw diet NOEC (mortality & sub-lethal effects) = 5760 mg a.i./kg dw diet	Practically non-toxic	1504815
Mallard duck (*Anas platyrhynchos*)	Dietary (5- day)	metofluthrin	LC_{50} > 5760 mg a.i./kg dw diet NOEC (sub-lethal effects) = 3120 mg a.i./kg dw diet	Practically non-toxic	1504816
Rat	Acute (4- hour inhalation, nose only)	metofluthrin	LC_{50} = 862-2030 mg a.i./m^3 air equivalent to: 0.862- 2.030 mg a.i./L air	Slightly acutely toxic	1504749

Organism	Study type	Test substance	Endpoint value	Degree of toxicity [a]	Reference (PMRA#)
Aquatic Organisms					
Invertebrate (*Daphnia magna*)	Acute (48-hour)	metofluthrin	EC_{50} = 4.7 µg a.i./L NOEC (sub-lethal effects) = 3.0 µg a.i./L	Very highly toxic	1504810
Rainbow trout (*Oncorhynchus mykiss*)	Acute (96-hour)	metofluthrin	LC_{50} = 1.2 µg a.i./L NOEC (mortality & sub-lethal effects) = 0.71 µg a.i./L	Very highly toxic	1504811
Bluegill sunfish (*Lepomis macrochirus*)	Acute (96-hour)	metofluthrin	LC_{50} = 2.7 µg a.i./L NOEC (sub-lethal effects) = 1.3 µg a.i./L	Very highly toxic	1630830
Carp (*Cyprinus carpio*)	Acute (96-hour)	metofluthrin	LC_{50} = 2.61 µg a.i./L NOEC (mortality & sub-lethal effects) = 0.712 µg a.i./L	Very highly toxic	1504812

Table 9 Toxic Substances Management Policy Considerations

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Metofluthrin endpoints
Toxic or toxic equivalent as defined by the *Canadian Environmental Protection Act*[1]	Yes		Yes
Predominantly anthropogenic[2]	Yes		Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	Metofluthrin DT_{50}: 2.9-3.4 days Transformation products: MFOA-D DT_{50}: 13.4-18.2 days TFPA DT_{50}: 6.2-76.9 days
	Water	Half-life ≥ 182 days	N/A
	Sediment	Half-life ≥ 365 days	N/A
	Air	Half-life ≥ 2 days or evidence of long range transport	N/A But volatilisation is expected to be an important route of dissipation based on the vapour pressure (1.96×10^{-3} Pa at 25ºC) and the Henry's Law Constant ($1/H = 1.754 \times 10^{3}$)

TSMP Track 1 Criteria	TSMP Track 1 Criterion value	Metofluthrin endpoints
Bioaccumulation[4]	Log $K_{OW} \geq 5$	4.97 (*Z*-isomer) 5.04 (*E*-isomer)
	Bioconcentration factor ≥ 5000	110-120
	Bioaccumulation factor ≥ 5000	N/A
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?		No, does not meet TSMP Track 1 criteria.

[1]All pesticides will be considered toxic or toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the toxicity criterion may be refined if required (in other words, all other TSMP criteria are met).
[2]The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.
[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.
[4]Field data (for example, Bioaccumulation factors) are preferred over laboratory data (for example, Bioconcentration factors) which, in turn, are preferred over chemical properties (for example, log K_{OW}).

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	References
1504701	2007, Product Identity and Disclosure of Ingredients S-1264Z Technical Grade, DACO: 2.1,2.11.1 CBI
1504703	2004, Product Identity and Disclosure of Ingredients, DACO: 2.1,2.11.1 CBI
1504704	2004, Product Identity and Disclosure of Ingredients, DACO: 2.1,2.11.1 CBI
1504705	2005, Product Identity and Disclosure of Ingredients of S-1264 Technical Grade Amended Report to Replace MRID # 46407-01, DACO: 2.1,2.11.1 CBI
1504707	2007, Product Identity and Disclosure of Ingredients S-1264Z Technical Grade, DACO: 2.1,2.11.1 CBI
1504708	2007, Comparison of Original and New specifications for SumiOne Technical Grade, DACO: 2.11.1 CBI
1504709	2004, Description of Beginning Materials and Manufacturing Use Process for S-1264 & Description of Formulation of Impurities, DACO: 2.11.1,2.11.2,2.11.4 CBI
1504711	2007, Description of Materials Used to Produce S-1264ZR; Description of Production Process of S-1264ZR; Description of Foramtion Impurities S-1264ZR (metofluthrin, SumiOne Technical Grade), DACO: 2.11.2,2.11.3,2.11.4 CBI
1504713	2007, Submission of statement of product specification form-SumiOne Technical Grade, DACO: 2.12,2.12.2 CBI
1504714	2005, Certification of Ingredient Limits of S-1264 Technical Grade-Amended, DACO: 2.12.1 CBI
1504716	2004, Certification of Ingredient Limits of S-1264 Technical Grade, DACO: 2.12.1 CBI
1504718	2002, Preliminary Analysis of S-1264 Technical Grade, DACO: 2.13,2.13.1,2.13.2 CBI
1504720	2007, Enforcement Analytical Methods of S-1264ZR Technical Grade, DACO: 2.13.1,2.13.2 CBI
1504722	2002, Enforcement Analytical Methods of S-1264 Technical Grade, DACO: 2.13.1,2.13.2 CBI
1504724	2007, Preliminary Analysis of S-1264ZR Technical Grade, DACO: 2.13.2,2.13.3 CBI
1504726	2003, Determination of Physical -Chemical Properties of S-1264, DACO: 2.14,2.14.1,2.14.2,2.14.3,2.14.6,3.5.11,3.5.12,3.5.13,3.5.7,3.5.8,3.5.9 CBI
1504727	2004, Calculation of Henrys Law Constant of S-1264, DACO: 2.14.10
1504728	2003, Determination of Dissociation Constant (pK[alpha])- S-1264, DACO: 2.14.10 CBI
1504729	2003, Determination of n-Octanol/Water Partition Coefficient- S-1264, DACO: 2.14.11 CBI

1504730 2004, Determination of Freezing Point, Solvent Solubility, Absorption Spectra and Autoflammability of S-1264, DACO: 2.14.12,2.14.4,2.14.8,3.5.11 CBI
1504731 2003, Determination of UV/Visible Absorption and boiling Point of S-1264, DACO: 2.14.12,2.14.5 CBI
1504732 2004, Stability of S-1264 Technical Grade to Normal and Elevated Temperatures, Metals and Metal Ions, DACO: 2.14.13 CBI
1504733 2007, Accerated Storage Stability of S-1264ZR Technical Grade, DACO: 2.14.14 CBI
1504734 2004, Storage Stability of S-1264 Technical Grade, DACO: 2.14.14 CBI
1504735 2004, Stability in Air of MFFO, DACO: 2.14.14 CBI
1504736 2004, Stability in Air of S-1264, DACO: 2.14.14 CBI
1504737 2003, Determination of Water Solubility- S-1264, DACO: 2.14.7 CBI
1504738 2004, Determination of Vapor Pressure, DACO: 2.14.9 CBI
1504739 2004, Summary of Physical/Chemical Properties, DACO: 2.16 CBI
1527995 2007, Product Identification of SumiOne TG, DACO: 2.1,2.15,2.2,2.3,2.4,2.5,2.6,2.7,2.8,2.9 CBI
1630827 2007, Enforcement Analytical Methods of S-1264ZR Technical Grade, DACO: 2.13.1,2.13.2,2.13.3 CBI
1836710 2009, Product ID and Disclosure of Ingredients of S-1264Z TG REVISED, DACO: 2.11 CBI
1836712 2007, Revised Description of Materials Used to (CBI removed), DACO: 2.11.2,2.11.3,2.11.4 CBI
1836713 2009, SPSF SumiOne TG, DACO: 2.12.2 CBI
1836714 2009, Revised Analytical Methods of S-1264ZR TG, DACO: 2.13.1 CBI
1836715 2009, Revised Preliminary Analysis of S-1264ZR TG, DACO: 2.13.3 CBI
1836716 2009, Metofluthrin: Evaluation of Selected Phys Chem Properties, DACO: 2.14.1,2.14.12,2.14.2,2.14.4,2.14.5,2.14.6 CBI
1836718 2009, Certification Odour, DACO: 2.14.3 CBI
1836719 2009, Analytical Standard, DACO: 2.15 CBI
1836720 2007, Comparison of Original and New Specification for SumiOne TG, DACO: 2.11.1 CBI
1851009 2010, Stability of SumiOne-Z and S-1264 Technical Grade to Normal and Elevated Temperatures, Metals, and Ions, DACO: 2.14.13 CBI
1907800 2010, DACO 2.13.1 Required Clarification, DACO: 2.13.1 CBI
1907801 2010, Clarification Reply-2.14.7, DACO: 2.14.7 CBI
1907802 2010, Clarification Reply-2.14.7, DACO: 2.14.7 CBI
1504797 2007, Bioaccumulation Test of S-1264 in Carp (Final Report), DACO: 8.2.2.4,9.5.6 CBI
1504813 2002, Bioaccumulation Test of S-1264 in Carp (Final Report), DACO: 8.2.2.4,9.5.6 CBI
1836732 2009, Metofluthrin: Development and Validation of an Analytical Method for the Determination of Metofluthrin in Soil, DACO: 8.2.2.1 CBI
1836733 2009, Analytical Method for SumoneZ Soil Metabolites Residues WAIVER, DACO: 8.2.2.1 CBI
1836734 2009, Metofluthrin: Independent Lab Validation of an Analytical Method for Biota Fish, DACO: 8.2.2.4 CBI
1836737 2009, CDS, DACO: 8.2.2.1 CBI

1836739 2009, Comprehensive Data Summary for Biota Analytical Method, DACO: 8.2.2.4 CBI
1907803 2010, Clarification Reply-DACO 8.2.2, DACO: 8.2.2 CBI
1907804 2010, Clarification Reply-DACO 8.2.2, DACO: 8.2.2 CBI
1907805 2010, Clarification Reply-DACO 8.2.2, DACO: 8.2.2 CBI
1508751 2007, Physical and Chemical Characteristics of Norm-1 Minus Substrate, DACO: 3.5 CBI
1508762 2007, Physical and Chemical Properties, Container Material and Description for the Outer Holder and the Refill for OFF! Clip On Insect Repellent, DACO: 3.5.5 CBI
1832931 2009, Deficiency Response #2 Regarding Starting Materials, DACO: 3.2.1 CBI
1832933 2009, Deficiency Response #1 Regarding Formulation Process, DACO: 3.2.2 CBI
1832934 2009, Updated Description of Formation of Impurities of Toxicological Concern, DACO: 3.2.3 CBI
1832936 2009, Updated Certified Limits Document, DACO: 3.3.1 CBI
1832941 2009, Submitting Updated Analytical Method, DACO 3.4.1 CBI
1832942 2009, Norm-1-Explanation for Two Peaks in the Analytical Method, DACO 3.4.1
1832943 2009, Storage Stability and Corrosion Characteristics Testing of NORM-1, DACO: 3.5.10 CBI
1832944 2009, Flammability, DACO: 3.5.11 CBI
1832945 2009, Corrosion Characteristics, DACO: 3.5.14 CBI
1832946 2009, Viscosity, DACO: 3.5.9 CBI
1907306 2010, Gas Chromatographic Determination of Metofluthrin (SumiOne) or Metofluthrin-Z (SumiOne-ZR) (CBI removed) DACO: 3.4.1 CBI
1907307 Analytical method responses to PMRA, DACO: 3.4.1 CBI

2.0 Human and Animal Health

1504698 2006, Metofluthrin: Report of the Cancer Assessment Review Committee. Evaluation of the Carcinogenic Potential of Metofluthrin. PC Code 109709, DACO: 12.5.4
1504700 2007, SumiOne Technical Grade: Comprehensive Data Summaries, DACO: 12.7
1504742 2004, Acute Oral Toxicity Study of MFFO in Rats, DACO: 4.2.1
1504743 2002, Acute Oral Toxicity Study of S-1264 in Rats, DACO: 4.2.1
1504744 2006, Acute Oral Toxicity Study of S-1264ZR in Rats, DACO: 4.2.1
1504745 2004, Acute Dermal Study of S-1264 of MFFO in Rats, DACO: 4.2.2
1504746 2002, Acute Dermal Toxicity Study of S-1264 in Rats, DACO: 4.2.2
1504747 2006, Acute Dermal Toxicity Study of S-1264ZR in Rats, DACO: 4.2.2
1504748 2002, Acute Inhalation Toxicity Study of S-1264 in Rats, DACO: 4.2.3
1504749 2006, Acute Inhalation Toxicity Study of S-1264ZR in Rats, DACO: 4.2.3
1504750 2006, Eye Irritation Test of S-1264ZR in Rabbits, DACO: 4.2.4
1504751 2001, Skin and Eye Irritation Tests of S-1264 in Rabbits, DACO: 4.2.4,4.2.5
1504752 2006, Skin Irritation Test of S-1264Zr in Rabbits, DACO: 4.2.5
1504753 2004, Primary Skin Irritation Test of MFFO in Rabbits, DACO: 4.2.5
1504754 2006, Skin Sensitization Test of S-1264ZR in Guinea Pigs (Maximization Test), DACO: 4.2.6
1504755 2004, Skin Sensitization Test of MFFO in Guinea Pigs, DACO: 4.2.6

1504756 2002, Skin Sensitization Test of S-1264 in Guinea Pigs (Maximization Test), DACO: 4.2.6
1504757 2004, The Dose Finding Study for Absence of Clinical Signs by Single Dermal Administration of S-1264 in Rats, DACO: 4.2.9
1504758 2003, S-1264: 13-week Repeated Dose Oral Toxicity (Feeding) Study in the Wistar Rat, DACO: 4.3.1
1504759 2004, S-1264: 13-Week Repeated Dose Oral Toxicity (Feeding) Study in the CD-1 Mouse, DACO: 4.3.1
1504760 2002, 90-day Oral toxicity Study with S-1264 in Beagle Dogs Followed by 42-day Recovery Study. Final Report., DACO: 4.3.2
1504761 2004, 12-month Repeated Dose Oral Toxicity Study of S-1264 in Dogs, DACO: 4.3.2
1504762 2002, One-Month Oral Toxicity Study of S-1264 in Rats, DACO: 4.3.3
1504763 2004, A 90-Day Repeated Dose Dermal Toxicity Study of S-1264 in Rats, DACO: 4.3.4,4.3.5
1504764 2002, Four-Week Repeated Inhalation Toxicity Study of S-1264 in Rats, DACO: 4.3.6,4.3.7
1504765 2006, Four-Week Repeated Inhalation Toxicity Study of S-1264ZR in Rats, DACO: 4.3.7
1504766 2006, Study for Mode of Action of S-1264 for Liver Tumor Promotion in Rats (In Vitro Effect of S-1264 on Cytochrome P450 Activity and mRNA level), DACO: 4.3.8
1504767 2006, SCC Comments on Cancer Assessment Comment: Evaluation of Carcinogenic Potential of Metofluthrin by USEPA Office of Pesticide Programs Cancer Assessment Review Committee, DACO: 4.3.8
1504768 2002, Six-Month Oral Toxicity Study of S-1264 in Rats, DACO: 4.3.8
1504769 2007, An Evaluation of the Human Relevance of the Metofluthrin-Induced Liver Tumors in Rats Based on Mode of Action-Revised, DACO: 4.3.8
1504770 2006, Gene Expression Profiling Analysis of Early Phase of Treatment in the Liver from S-1264 -Treated Rats, DACO: 4.3.8
1504771 2006, The Evaluation of Human Relevance of the Metofluthrin-Induced Liver Tumors in Rats Based on Mode of Action, DACO: 4.3.8
1504772 2007, Pilot Study for Mode of Action of S-1264 for Liver Tumor Induction in Rats, DACO: 4.3.8
1504773 2005, Study for Mode of Action of S-1264 for Liver Tumor Promotion in Rats, DACO: 4.3.8
1504774 2006, The 2nd Study for Mode of Action of S-1264 for Liver Tumor Promotion in Rats, DACO: 4.3.8
1504775 2005, S-1264: 78-Week Oncogenicity (Feeding) Study in the CD-1 Mouse, DACO: 4.4.2,4.4.3
1504776 2005, S-1264: Combined Chronic Toxicity/Oncogenicity (Feeding) Study in the Rat, DACO: 4.4.1,4.4.4
1504777 2005, Oral (Diet) Two-Generation (One Litter per Generation) Reproduction Study of S-1264 in Rats, DACO: 4.5.1
1504778 2004, Oral (Gavage) Acute Neurotoxicity Study of S-1264 in Rats, DACO: 4.5.12

1504779 2005, Appendix G Testing Facility Positive Control Data for: Subchronic Neurotoxicity of S-1264 in Rats: Final Report MRID # 464067-29; Project Numbers QAT-0060 and 1119-033, DACO: 4.5.13
1504780 2004, Oral (Diet) Subchronic Neurotoxicity Study of S-1264 in Rats, DACO: 4.5.13
1504781 2002, Study for Effects on Pre- and Postnatal Development, Including Maternal Function of S-1264 Administered Orally to Rats, DACO: 4.5.2
1504782 2002, Study for Effects on Embryo-fetal Development of S-1264 Administered Orally to Rabbits, DACO: 4.5.2
1504783 2002, Study for Effects on Embryo-Fetal Development of S-1264 Administered Orally to Rats, DACO: 4.5.3
1504784 2004, Reverse Mutation Test of MFFO in Bacterial Systems, DACO: 4.5.4
1504785 2002, Reverse Mutation Test of S-1264 in Bacterial Systems, DACO: 4.5.4
1504786 2006, Reverse Mutation Test of S-1264ZR in Bacterial Systems, DACO: 4.5.4
1504787 2002, In Vitro Chromosomal Aberration Test on S-1264 in Chinese Hamster Lung Cells (CHL/IU), DACO: 4.5.5
1504788 2002, Micronucleus Test on S-1264 in Mice, DACO: 4.5.8
1504789 2004, The Disposition and Metabolism of [carbonyl-14C]S-1264 RTZ in Rats, DACO: 4.5.9
1504790 2002, The Disposition and Metabolism of [carbonyl-14C]S-1264RTE in Rats, DACO: 4.5.9
1504791 2002, The Disposition and Metabolism of [carbonyl-14C]S-1264RTZ (1R-trans-Z) after Repeated Administration in Rats, DACO: 4.5.9
1504792 2002, The Disposition and Metabolism of [methoxybenzyl-alpha-14C]S1264RTZ (1R-trans-Z) after Repeated Administration to Rats, DACO: 4.5.9
1504793 2002, The Disposition and Metabolism of Methoxybenzyl-alpha-14C]S-1264RTZ in Rats, DACO: 4.5.9
1504794 2002, Study of Fertility and Early Embryonic Development to Implantation of S-1264 Administered Orally to Rats, DACO: 4.8
1509556 2006, Metofluthrin: Second Report of the Cancer Assessment Review Committee, DACO: 12.5.4
1511924 2005, S-1264: 78-Week Oncogenicity (Feeding) Study in the CD-1 Mouse, DACO: 4.4.2,4.4.3
1512273 2005, S-1264: Combined Chronic Toxicity/Oncogenicity (Feeding) Study in the Rat, DACO: 4.4.1,4.4.4
1512275 2005, S-1264: Combined Chronic Toxicity/Oncogenicity (Feeding) Study in the Rat, DACO: 4.4.1,4.4.4
1512790 2005, Oral (Diet) Two-Generation (One Litter per Generation) Reproduction Study of S-1264 in Rats, DACO: 4.5.1
1697966 2007, SumiOne Technical Grade (USEPA Reg. No. 10308-30); metofluthrin): Metofluthrin: Second Report (July 26, 2007) of USEPA Cancer Review Committee, DACO: 12.5.4
1766418 2009, Extension and Waiver Request, DACO: 0.8
1836720 2007, Comparison of Original and New Specification for SumiOne TG, DACO: 2.11.1 CBI
1836721 2002, Disposition and Metabolism of carbonyl 14C S-1264 RTE rats, DACO: 4.5.9

1836722 2004, Disposition and Metabolism of carbonyl 14C S-1264 RTZ rats, DACO: 4.5.9

1836723 2009, Subchronic-Long Term Studies WAIVER Rationale to Address Deficiency, DACO: 4.4

1836724 2009, 90-Day Inhalation Study WAIVER Rationale Submitted to Address Deficiency, DACO: 4.3.6

1836725 2009, Additional Data on 4 Week Repeated Inhalation Tox Tests on Old & New S1264 Rats, DACO: 4.3.6,4.3.7

1836726 2009, Historical Control Data on Non-Neoplastic Findings on the CD-1 Strain of Mice in Onco Study, DACO: 4.4.2

1836727 2004, Oral Diet Dosage-Range Reproduction Study of S1264 in Rats, DACO: 4.5.1

1836728 2004, Oral Diet Dosage-Range Reproduction Study of S1264 in Rats, DACO: 4.5.1

1836729 2004, Oral Diet Dosage-Range Reproduction Study of S1264 in Rats-Form Sample Analysis, DACO: 4.5.1

1836730 2009, In Vitro Chromosomal Aberration Test on S1264 in CHA Lung Expos Time, DACO: 4.5.6

1836731 2009, Two Positive Control Neurotoxicity Studies with CRL:CD Rats, DACO: 4.5.12

2005945 2011, Introduction to Historical Control Data on Liver Neoplastic Findings (Hepatocellular adenoma and Hepatocellular carcinoma) in Hsd:RccHan: WIST, Wistar Hannover Rats, DACO: 4.4.4

2005946 2001, Historical Control Data on Liver Neoplastic Findings (Hepatocellular adenoma and Hepatocellular Carcinoma) in Hsd:RccHan: WIST, Wistar Hannover Rats, DACO: 4.4.4

2009011 2011, Sexual Maturation Historical Control Data, DACO: 4.5.1

2009013 2011, Incidence of Histomorphic Observations in P Generations Female Rats Diet Studies 2000 - 2008, DACO: 4.5.1

2009014 2011, Summary of Maternal Necropsy Observations, DACO: 4.5.1

1508780 2007, Exposure Summary, DACO: 5.1 CBI

1508781 2007, Exposure Summary, DACO: 5.1 CBI

1508782 2004, Measurement of Air Concentration and Deposition on Cotton Dosimeters of Metofluthrin Generated by a Personal Outdoor Insect Repellent Device in an Outdoor Environment, DACO: 5.14

1841115 2009, Use Description Scenario (Application and Post Application) Deficiency Response, DACO 5.2

1841116 2009, Mixer/Loader/Applicator Deficiency Response, DACO 5.3,5.4,5.5

1841117 2009, Passive Dosimtery Air Monitoring Deficiency Responses, DACO: 5.6,5.7 CBI

1841118 2009, Passive Dosimtery Air Monitoring Deficiency Responses, DACO: 5.6,5.7 CBI

1841119 2009, Calculation Tables for Golden Pacific Study 040166, Attachment to Study Title: Measurement of Air Concentration and Deposition on Cotton Dosimeters of Metofluthrin Generated by a Personal Outdoor Insect Repellent Device in an Outdoor Environment, DACO: 5.6

1841120 2009, 5.6B Raw Data for R&D 02, DACO: 5.6(B) CBI

1841121 2009, 5.6B Raw Data for R&D 02A, DACO 5.6(B) CBI
1841122 2009, 5.6B Raw Data for R&D 02B, DACO 5.6(B) CBI
1841123 2009, 5.6B Raw Data for R&D 03, DACO 5.6(B) CBI
1841124 2009, 5.6B Raw Data for MT-10, DACO 5.6(B) CBI
1841125 2009, 5.6B Raw Data for MT-11, DACO 5.6(B) CBI
1841126 2009, 5.6B Raw Data for MT-12, DACO 5.6(B) CBI
1841127 2009, 5.6B Raw Data for MT-13, DACO 5.6(B) CBI
1841128 2009. 5.6B Raw Data for MT-14, DACO 5.6(B) CBI
1841129 2009, 5.6B Raw Data for MT-15, DACO 5.6(B) CBI
1841130 2009, 5.6B Raw Data for MT-16, DACO 5.6(B) CBI
1841131 2009, 5.6B Raw Data for MT-17, DACO 5.6(B) CBI
1841132 2009, 5.6B Raw Data for MT-18, DACO 5.6(B) CBI
1841133 2009, 5.6B Raw Data for R&D 02, DACO 5.6(B) CBI
1841134 2009, 5.6B Raw Data for R&D 02A, DACO 5.6(B) CBI
1841135 2009, 5.6B Raw Data for R&D 02B, DACO 5.6(B) CBI
1841136 2009, 5.6B Raw Data for R&D 03, DACO 5.6(B) CBI
1841137 2009, 5.6B Raw Data for MT-10, DACO 5.6(B) CBI
1841138 2009, 5.6B Raw Data for MT-11, DACO 5.6(B) CBI
1841139 2009, 5.6B Raw Data for MT-12, DACO 5.6(B) CBI
1841140 2009, 5.6B Raw Data for MT-13, DACO 5.6(B) CBI
1841141 2009, 5.6B Raw Data for MT-14, DACO 5.6(B) CBI
1841142 2009, 5.6B Raw Data for MT-15, DACO 5.6(B) CBI
1841143 2009, 5.6B Raw Data for MT-16, DACO 5.6(B) CBI
1841144 2009, 5.6B Raw Data ta for MT-17, DACO 5.6(B) CBI
1841145 2009, 5.6B Raw Data for MT-18, DACO 5.6(B) CBI
1841146 2009, OFF! Clip On – Metofluthrin Release Rate From The Device And Emission, DACO 5.9

3.0 Environment

1504744 2006, Acute Oral Toxicity Study of S-1264ZR in Rats, DACO: 4.2.1
1504749 2006, Acute Inhalation Toxicity Study of S-1264ZR in Rats, DACO: 4.2.3
1504797 2007, Bioaccumulation Test of S-1264 in Carp (Final Report), DACO: 8.2.2.4,9.5.6
1504798 2004, Hydrolysis of [14C]S-1264 at pH 4, 7 and 9, DACO: 8.2.3.2
1504799 2004, Metofluthrin Aerobic Soil Metabolism (Supplemental Information), DACO: 8.2.3.4.2
1504800 2006, Metofluthrin Aerobic Soil Metabolism-Raw Data and Calculations, DACO: 8.2.3.4.2
1504802 2003, Aerobic Soil Metabolism Study of [14C]S-1264, DACO: 8.2.3.4.2
1504804 2004, Soil Adsorption/Desorption of [14C]S-1264 by the Batch Equilibrium Method, DACO: 8.2.4.2
1504810 2004, S-1264- Acute Toxicity to Water Fleas (*Daphnia magna*) Under Flow-Through Conditions, DACO: 9.3.2
1504811 2004, S-1264- Acute Toxicity to Rainbow Trout (*Oncorhynchus mykiss*) Under Flow-Through Conditions, DACO: 9.5.2.1

1504812 2002, [methoxymethylbenzyl-alpha-14C]S-1264: Acute toxicity Test With Common Carp (*Cyprinus carpio*) Under Flow-Through Conditions, DACO: 9.5.2.3
1504814 2003, An Acute Oral Toxicity Study with the Northern Bobwhite, DACO: 9.6.2.1
1504815 2003, A Dietary LC50 Study with the Northern Bobwhite, DACO: 9.6.2.4
1504816 2003, A Dietary LC50 Study with the Mallard, DACO: 9.6.2.5
1630829 2008, Acute Contact Toxicity Test of S-1264, DACO: 9.2.4.1
1630830 2008, S-1264 Technical Grade-Acute Toxicity to Bluegill Sunfish (*Lepomis macrochirus*) Under Flow-Through Conditions Following FIFRA Guideline 72-1, OPPTS Draft Guideline 850.1075, OECD Guideline 203 and the Official Journal of the European Communities Annex V – Method C.1., DACO: 9.5.2.2

4.0 Value

1508720 Value Summary, DACO: 10.1
1508724 2007, Evaluation and optimisation of Bunny device voltage, substrate thickness and active ingredient dosage to deliver metofluthrin to repel mosquitoes in the field, DACO: 10.2.3.3
1508726 2007, Determining the efficacy of Norm-1 in the field against a biting population of mosquitoes, DACO: 10.2.3.3
1508731 2007, Evaluation of an insect repellant: Efficacy testing of the Airepod-1 Insect Repellant in the field against a biting population of mosquitoes (*Culicidae*), DACO: 10.2.3.3
1836700 2009, Comparison of Efficacy of SumiOne-Z (S-1264-Z) with SumiOne (S-1264), DACO: 10.2.3.1

B. Additional Information Considered

i) Published Information

1.0 Human and Animal Health

2007551 Kim, Kyu-Bong et al., 2010, Age, Dose, and Time Dependency of Plasma and Tissue Distribution of Deltamethrin in Immature Rats - Toxicological Sciences, Volume 115, Number 2, Pages 354 to 368, DACO: 4.5.9
2050136 Scollon, Edward, 2010, Pyrethroids: Evaluation of Data from Developmental Neurotoxicity Studies and Consideration of Comparative Sensitivity, DACO: 4.5.14
2409268 U.S. EPA (2012a). Standard Operating Procedures for Residential Pesticide Exposure Assessment. EPA: Washington, DC. Revised October 2012.